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(57) Abstract Nucleic acids encoding mammalian, e.g., human receptors, purified receptor proteins and fragments thereof. Antibodies, both polyclonal and monoclonal, are also provided. Methods of using the compositions for both diagnostic and therapeutic utilities are provided.			

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HUMAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

FIELD OF THE INVENTION

The present invention relates to compositions and methods for affecting mammalian physiology, including, e.g., morphogenesis or immune system function. In particular, it provides nucleic acids, proteins, and antibodies, e.g., which regulate development and/or the immune system along with related reagents and methods. Diagnostic and therapeutic uses of these materials are also disclosed.

BACKGROUND OF THE INVENTION

Recombinant DNA technology refers generally to techniques of integrating genetic information from a donor source into vectors for subsequent processing, such as through introduction into a host, whereby the transferred genetic information is copied and/or expressed in the new environment. Commonly, the genetic information exists in the form of complementary DNA (cDNA) derived from messenger RNA (mRNA) coding for a desired polypeptide product. The carrier is frequently a plasmid having the capacity to incorporate cDNA for later replication and/or expression in a host and, in some cases, actually to control expression of the cDNA and thereby direct synthesis of the encoded product in the host.

For some time, it has been known that the mammalian immune response is based on a series of complex cellular interactions, called the "immune network". Recent research has provided new insights into the inner workings of this network. While it remains clear that much of the immune response does, in fact, revolve around the network-like interactions of lymphocytes, macrophages, granulocytes, and other cells, immunologists now generally hold the opinion that soluble proteins, known as lymphokines, cytokines, or monokines, play critical roles in controlling these cellular interactions. Thus, there is considerable interest in

the isolation, characterization, and mechanisms of action of cell modulatory factors, an understanding of which will lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g.,

5 immune system disorders.

Lymphokines apparently mediate cellular activities in a variety of ways. They have been shown to support the proliferation, growth, and/or differentiation of pluripotential hematopoietic stem cells into vast numbers 10 of progenitors comprising diverse cellular lineages which make up a complex immune system. Proper and balanced interactions between the cellular components are necessary for a healthy immune response. The different cellular lineages often respond in a different manner 15 when lymphokines are administered in conjunction with other agents.

Cell lineages especially important to the immune response include two classes of lymphocytes: B-cells, which can produce and secrete immunoglobulins (proteins 20 with the capability of recognizing and binding to foreign matter to effect its removal), and T-cells of various subsets that secrete lymphokines and induce or suppress the B-cells and various other cells (including other T-cells) making up the immune network. These lymphocytes 25 interact with many other cell types.

Another important cell lineage is the mast cell (which has not been positively identified in all mammalian species), which is a granule-containing connective tissue cell located proximal to capillaries 30 throughout the body. These cells are found in especially high concentrations in the lungs, skin, and gastrointestinal and genitourinary tracts. Mast cells play a central role in allergy-related disorders, particularly anaphylaxis as follows: when selected 35 antigens crosslink one class of immunoglobulins bound to receptors on the mast cell surface, the mast cell degranulates and releases mediators, e.g., histamine, serotonin, heparin, and prostaglandins, which cause allergic reactions, e.g., anaphylaxis.

Research to better understand and treat various immune disorders has been hampered by the general inability to maintain cells of the immune system in vitro. Immunologists have discovered that culturing many 5 of these cells can be accomplished through the use of T-cell and other cell supernatants, which contain various growth factors, including many of the lymphokines.

The interleukin-1 family of proteins includes the IL-1 α , the IL-1 β , the IL-1RA, and recently the IL-1 γ , 10 (also designated Interferon-Gamma Inducing Factor, IGIF). This related family of genes has been implicated in a broad range of biological functions. See Dinarello (1994) FASEB J. 8:1314-1325; Dinarello (1991) Blood 77:1627-1652; and Okamura, et al. (1995) Nature 378:88-15 91.

From the foregoing, it is evident that the discovery and development of new soluble proteins and their receptors, including ones similar to lymphokines, should contribute to new therapies. A number of degenerative or 20 abnormal conditions directly or indirectly involve development, differentiation, or function, e.g., of the immune system and/or hematopoietic cells. In particular, the discovery and understanding of novel receptors for lymphokine-like molecules which enhance or potentiate the 25 beneficial activities of other lymphokines, would be highly advantageous. The present invention provides new receptors for ligands exhibiting similarity to interleukin-1 like compositions and related compounds, and methods for their use.

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SUMMARY OF THE INVENTION

The present invention is directed to novel receptors related to IL-1 receptors and their biological activities. These receptors, e.g., primate or rodent, 35 are designated IL-1 receptor like molecular structures, IL-1 Receptor DNAX designation 8(IL-1RD8), IL-1 Receptor DNAX designation 9(IL-1RD9) and IL-1 Receptor DNAX designation 10(IL-1RD10). The invention includes nucleic acids coding for the polypeptides themselves and methods

for their production and use. The nucleic acids of the invention are characterized, in part, by their homology to cloned complementary DNA (cDNA) sequences enclosed herein.

5 In certain embodiments, the invention provides a composition of matter selected from the group of: an isolated or recombinant IL-1RD8 polypeptide comprising a segment of at least 12 contiguous amino acids of SEQ ID NO: 2 or 4, a natural sequence IL-1RD8 polypeptide comprising SEQ ID NO: 2 or 4, a fusion protein comprising IL-1RD8 sequence; an isolated or recombinant IL-1RD9 polypeptide comprising at least 12 contiguous amino acids of SEQ ID NO: 6, 8, 10, 12, 14, or 16; a natural sequence IL-1RD9 comprising SEQ ID NO: 6, 8, 10, 12, 14, or 16; a 10 fusion protein comprising IL-1RD9 sequence; an isolated or recombinant IL-1RD10 polypeptide comprising at least 12 contiguous amino acids of SEQ ID NO: 18 or 20; a natural sequence IL-1RD10 comprising SEQ ID NO: 18 or 20; and a fusion protein comprising IL-1RD10 sequence. In 15 various embodiments, the recombinant or isolated polypeptide comprises a segment identical to a corresponding portion of an IL-1RD8, as described, wherein: the number of contiguous amino acid residues is: at least 17 amino acids; at least 21 amino acids; or at least 25 amino acids; or to a corresponding portion of an IL-1RD9, as described, wherein the number of identical contiguous amino acid residues is: at least 17 amino acids; at least 21 amino acids; or at least 25 amino acids; or of an IL-1RD10, as described, wherein the 20 number of identical contiguous amino acid residues is: at least 17 amino acids; at least 21 amino acids; or at least 25 amino acids.

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In polypeptide embodiments, the invention provides a composition of matter wherein the IL-1RD8 comprises a mature sequence shown in SEQ ID NO: 2 or 4; an IL-1RD9 that comprises a mature sequence shown in SEQ ID NO: 6, 8, 10, 12, 14 or 16; an IL-1RD10 that comprises a mature sequence shown in SEQ ID NO: 18 or 20; or the IL-1RD8, IL-1RD9, or IL-1RD10 polypeptide: is from a warm blooded

animal, e.g., a primate, such as a human; comprises at least one polypeptide segment of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, or 20; exhibits a plurality of portions having segments identical to specific sequence identifiers; is a natural allelic variant of a primate IL-1RD8; a primate or rodent IL-1RD9; or a primate IL-1RD10; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes that are specific for: a primate IL-1RD8, a primate or rodent IL-1RD9, or primate IL-1RD10; exhibits a sequence identity over a length of at least about 20 amino acids to: a primate IL-1RD8, a primate or rodent IL-1RD9, or a primate IL-1RD10; has a molecular weight of at least 100 kD with natural glycosylation; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence. Certain preferred embodiments include compositions comprising: a sterile IL-1RD8, IL-1RD9, or IL-1RD10 polypeptide; or the IL-1RD8, IL-1RD9, or IL-1RD10 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile IL-1RD8, IL-1RD9, or IL-1RD10 polypeptide; or the IL-1RD8, IL-1RD9, or IL-1RD10 polypeptide, as described, and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

Certain fusion proteins are provided, e.g., comprising: mature polypeptide sequence shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 or 20; a detection or purification tag, including a FLAG, His6, or Ig sequence; or sequence of another receptor protein. Kit embodiments include a kit comprising such a polypeptide, and: a compartment comprising the polypeptide; and/or instructions for use or disposal of reagents in the kit.

In binding compound embodiments, the invention provides a binding compound comprising an antigen binding site from an antibody, which specifically binds to a natural: IL-1RD8, IL-1RD9, or IL-1RD10 polypeptide, 5 wherein: the polypeptide is a primate or rodent protein; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised to a polypeptide sequence of a mature polypeptide comprising a sequence 10 sequence shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 or 20; is raised to a mature primate or rodent IL-1RD8; is raised to a purified human IL-1RD8; is raised to a purified mouse IL-1RD9; is immunoselected; is a polyclonal antibody; binds to a denatured IL-1RD8, IL- 15 1RD9, or IL-1RD10; exhibits a Kd to antigen of at least 30 μ M; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label; IL-1RD9 protein, wherein: the 20 polypeptide is a primate or rodent protein; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised against a polypeptide sequence of a mature polypeptide comprising a sequence sequence shown 25 in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 or 20; is raised against a mature primate IL-1RD9; is raised to a purified human IL-1RD9; is immunoselected; is a polyclonal antibody; binds to a denatured IL-1RD9; exhibits a Kd to antigen of at least 30 μ M; is attached 30 to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label; IL-1RD10 protein, wherein: the polypeptide is a primate or rodent protein; the binding compound is an Fv, Fab, or 35 Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised against a polypeptide sequence of a mature polypeptide comprising a sequence sequence shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 or 20; is raised against a

mature primate IL-1RD10; is raised to a purified human IL-1RD10; is immunoselected; is a polyclonal antibody; binds to a denatured IL-1RD10; exhibits a K_d to antigen of at least 30 μM ; is attached to a solid substrate,

5 including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label. Kits are provided, e.g., those comprising the binding compound, and: a compartment comprising the binding compound; and/or

10 instructions for use or disposal of reagents in the kit. Preferably, the kit is capable of making a qualitative or quantitative analysis.

Other embodiments include a composition comprising: a sterile binding compound, or the binding compound and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

Nucleic acid embodiments include an isolated or recombinant nucleic acid encoding a polypeptide or fusion protein, wherein: the IL-1RD8, IL-1RD9, or IL-1RD10 is from a mammal; said nucleic acid: encodes an antigenic polypeptide sequence shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 or 20; encodes a plurality of antigenic polypeptide sequences shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 or 20; exhibits at least about 30 nucleotides to a natural cDNA encoding the segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a mammal, including a primate; comprises a natural full length coding sequence; is a hybridization probe for a gene encoding said IL-1RD8, IL-1RD9, or IL-1RD10; comprises a plurality of nonoverlapping segments of at least 15, 18, 21, or 25 nucleotides shown in SEQ ID NO: 1, 3, 5, 7, 9 11, 13, 15, 17, 19; or is a PCR primer, PCR product, or mutagenesis primer. The invention further provides a cell comprising

such a recombinant nucleic acid, e.g., where the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell. Certain kit

5 embodiments include a comprising the nucleic acid, and: a compartment comprising the nucleic acid; a compartment further comprising: a primate IL-1RD8, a primate or rodent IL-1RD9, or a primate IL-1RD10 polypeptide; and/or instructions for use or disposal of reagents in the kit.

10 Preferably, the kit is capable of making a qualitative or quantitative analysis.

In other nucleic acid embodiments, the nucleic acid is one which: hybridizes under wash conditions of 40° C and less than 2M salt to either SEQ ID NO: 1, 3, 5, 7, 9, 15 11, 13, 15, 17, or 19; or exhibits identity over a stretch of at least about 30 nucleotides to a primate IL-1RD8, a primate or rodent IL-1RD9, or a primate IL-1RD10. In various preferred embodiments: the wash conditions are: at 45° C and/or 500 mM salt; at 55° C and/or 150 mM 20 salt; or the stretch is at least 55 nucleotides; or at least 75 nucleotides.

Methods of modulating physiology or development of a cell or tissue culture cells are provided, e.g., comprising contacting the cell with an agonist or 25 antagonist of a primate IL-1RD8, a primate or rodent IL-1RD9, or a primate IL-1RD10. Preferably, the cell is transformed with a nucleic acid encoding either IL-1RD8, IL-1RD9, or IL-1RD10, and another IL-1R.

30 DETAILED DESCRIPTION OF THE INVENTION

I. General

The present invention provides the amino acid sequence and DNA sequence of mammalian, herein, e.g., primate and rodent IL-1 receptor-like molecules; these 35 molecules IL-1 Receptor DNAX designation 8(IL-1RD8), IL-1 Receptor DNAX designation 9(IL-1RD9) and IL-1 Receptor DNAX designation 10(IL-1RD10) having particular defined properties, both structural and/or biological. These embodiments increase the number of members of the human

IL-1 receptor-like family from 7 to at least 10. These receptors have been numbered internally as DNAX designations D1, D2, D3, D4, D5, D6, and now D8, D9, and D10, and are referred to as IL-1RD1 through D10. Various 5 cDNAs encoding these molecules were obtained from primate, e.g., human, or rodent, e.g., mouse, cDNA sequence libraries. Other primate, rodent, or other mammalian counterparts would also be desired.

Some of the standard methods applicable are 10 described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al. Biology, 15 Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York; each of which is incorporated herein by reference.

A partial nucleotide and corresponding amino acid 20 sequence of a human IL-1RD8 coding segment is shown in SEQ ID NO: 1 and 2, respectively. Supplemental human IL-1RD8 nucleotide and corresponding sequence is provided in SEQ ID NO: 3 and 4, respectively.

Similarly for primate IL-1RD9, partial nucleotides 25 (SEQ ID NO: 5) and corresponding amino acid sequences (SEQ ID NO: 6) of a primate IL-1RD9 coding segment are provided. Supplemental primate IL-1RD9 is provided in SEQ ID NO: 7, 8, 9, and 10. Rodent embodiments of IL-1RD9 are provided in SEQ ID NO: 11, 12, with supplemental 30 IL-1RD9 rodent sequence in SEQ ID NO: 13, 14, 15, and 16.

For an embodiment of human IL-1RD10, a partial nucleotide and corresponding partial amino acid sequence are provided in SEQ ID NO: 17 and 18, respectively, with supplemental human IL-1RD10 nucleotide and corresponding 35 partial amino acid sequence provided in SEQ ID NO: 19 and 20, respectively.

Some sequences provided lack some portions of these receptors, as suggested by alignment of sequences shown in Tables 1-4). Note the alignment of IL-1RD10 with IL-

1RD8 and D3s, which are alpha type receptor subunits.

Table 4 exhibits alignment of primate and rodent IL-1RD9.

It is to be understood that this invention is not limited to the particular methods, compositions and 5 receptors specifically embodied herein, as such methods, compositions and receptors may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the 10 present invention which is only limited by the appended claims.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the 15 art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, 20 patents, and other references mentioned herein are incorporated by reference in their entirety including all figures, graphs, and drawings.

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Table 1

Alignment of the extracellular domains of various IL-1Rs. hIL-1RD10 is SEQ ID NO: 20; hIL-1RD8 is SEQ ID NO: 3; mIL-1RD3 is GenBank X85999; hIL-1RD6 is GenBank U49065; rIL-1RD6 is GenBank 30 U49066; mIL-1RD4 is GenBank Y07519 and GenBank D13695; hIL-1RD4 is GenBank D12763; hIL-1RD2 is GenBank X59770; mIL-1RD2 is GenBank X59769; hIL-1RD5 is GenBank U43672; mIL-1RD5 is GenBank U43673; mIL-1RD1 is GenBank M20658, M29752; hIL-1RD1 is GenBank X16896; 35 CIL-1RD1 is GenBank 86325; and hFGR4 is GenBank P22455. Other species counterparts may be obtained from public sequence databases.

mIL-1RD3	MGLL WYLMSSLSFYG ILQSHASERC DDWLDTMR..
hIL-1RD6	M WSLLLCLGLSI ALPLSVTADG CKDIFMKN..
40 rIL-1RD6	MGM PPLLFCWVSF VLPLFVAAGN CTDVYMH..
mIL-1RD4	MI DRQRMLGLWAL AILTLPMYLT VTEGSKSS..
hIL-1RD4	MG FWILAILTIL MYSTAAKFSK QS.....
hIL-1RD2	MLRLYV LVMGVSAFTL QPAAHGTGAAR SCRFRGRHYK
mIL-1RD2	MFILLVLVTG VSAFTTPTVV HTGKVSESPI TSEKPTVHGD NCQFRGRREFK
45 hIL-1RD10
hIL-1RD5	MNCRE LPLTLWVLIS VSTAESCTSR PHITVVE...
mIL-1RD5	MHHEE LILTLCLILIV KSASKSCIHR SQIHVVE..
mIL-1RD1	MENMK VLLGLICLMLV PLLSLEIDVC TEYPNQIVLF
50 hIL-1RD1	MK VLLRLICFIA LLISSLEADK CKEREKIIIL
CIL-1RD1	MHKMT STFLLIGHLI LLIPLFSAEE CVICNYFVLV
hIL-1RD8	M KPPFLLALVV CSVVSTNLKM VSKRNSVDGC IDWSVDLKTY

	hFGR4	...MRLLLAL LGVLLSVPGP PVLSLEASEEE VELEPCLAPS LEQQEQELTV
	mIL-1RD3	QIQVFEDEPA RIKCPLFEHF LKYNYSTAHS SGLTLLWYWT RQDRDLEEPI
	hIL-1RD6	.EILSASQPF AFNCTFPPI.TS GEVSVTWYKNSSKIPV
5	rIL-1RD6	.EMISEGQPF PFNCTYPPV.TN GAVNLTHWRTPSKSPI
	mIL-1RD4	..WGLENEAL IVRCPQRG.R STYPVEWYYSDTNESI
	hIL-1RD4	..WGLENEAL IVRCPRQG.K PSYTVDWYYSQTNKSI
	hIL-1RD2	REFRLEGEPV ALRCPQVWY LWA....SVS PRINLTWHKNDSARTV
	mIL-1RD2	SELRLEGEPV VLRCPLAPHS DIS....SS SHSFLTWSKLDSSQLI
10	hIL-1RD10
	hIL-1RD5GEPFY LKHCSCSLAHEI ETTTKSWYKS ...SGSQEHV
	mIL-1RD5GEPFY LKPCGISAIVHRN ETATMRWFKG ...SASHEYR
	mIL-1RD1	LSV...NEID IRKCPLTPN.KM HGDTIIWYKNDSKTPI
	hIL-1RD1	VSS..ANEID VRPCPLNPN.E HKGTITWYKDDSKTPV
15	cIL-1RD1GEPT AISCVPVITL.PMLH SDYNLTWYRNGSNMPY
	hIL-1RD8	..MALAGEPV RVKCALFYSY IRTNYSTAQS TGLRLMWYKN ..KGDLEEPI
	hFGR4ALGQPV RLCCGRAERG G.....HWYKEGSRLAP
	mIL-1RD3	NFRLP..ENRI SKEKDVLWFR PTLLNDTGNY TCMLRNTTYC SKVAFPLEVV
20	hIL-1RD6	SKII..QSRI HQDETWLFL PMEWGDSGVY QCVIKGRDSC HRIHVNLTVF
	rIL-1RD6	SINR..HVRI HQDQSUILFL PLALEDSGIY QCVIKDAHSC YRIAINTLTVF
	mIL-1RD4	PTQK..RNRI FVSRDRKLKFL PARVEDSGIY ACVIRSPNLN KTGYLNVTIH
	hIL-1RD4	PTQE..RNRV FASGQLLKFL PAEVADSGIY TCIVRSPTFN RTGYANVTIY
	hIL-1RD2	PGE..ETRM WAQDGALWLL PALQEDSGTY VCTTRNASYC DKMSIELRVF
25	mIL-1RD2	PRDEP...RM WVKGNILWIL PAVQQDSGYT ICTFRNASHC EQMSVELKVF
	hIL-1RD10
	hIL-1RD5	ELNPRSSSRI ALHDCVLEFW PVELNDTGSY FFQMKN..YT QWKLNVIRR
	mIL-1RD5	ELNNRSPRIV TFHDHTLEFW PVEMEDEGY ISQVGN..DR RNWTLNVTKR
	mIL-1RD1	SADR..DSRI HQQNEHLWFW PAKVEDSGYY YCIVRNSTYC LTKVTVTBL
30	hIL-1RD1	STEQ..ASRI HQHKEKLWFW PAKVEDSGHY YCVRNNSYY LRIKISAKFV
	cIL-1RD1	TTER..RARI HQRKGLLWFI PAALEDSGLY ECEVRSLNRS KQKIIINLKVF
	hIL-1RD8	IFS...EVRM SKEEDSIWFH SAEAQDSGFY TCVLRNSTYC MKVMSMLTVA
	hFGR4	AG.....RV RGWRGRLEIA SFLPEDAGRY LCLARGSMIV LQNLTLITGD
35	mIL-1RD3	QK.....DSC FNSAMRFPVH KMYIEHGIHK
	hIL-1RD6	EK.....HWCDSIGG LP..NLSDEYK QILHLGKDDS
	rIL-1RD6	RK.....HWCDSNEE SSINSSDEYQ QWLPIGKSGS
	mIL-1RD4	KK.....PPSCN .IPDY..LMYS TVRGSDKNFK
	hIL-1RD4	KK.....QSDCN .VPDY..LMYS TVSGSEKNSK
40	hIL-1RD2	EN.....TDA FLPFI..SYP QILTLSTSGV
	mIL-1RD2	KN.....TEA SLPHV..SYL QISALSTTGL
	hIL-1RD10
	hIL-1RD5	NK.....HSC FTERQ..VTS KIVEVKKFFQ
	mIL-1RD5	NK.....HSC FSDKL..VTS RDVEVNKSLH
45	mIL-1RD1	EN.....DPGIC .YSTQ..ATFP QRLHIAGDGS
	hIL-1RD1	EN.....EPNLC .YNAQ..AIFK QKLPVAGDGG
	cIL-1RD1	KN.....DNGLC .FNGE..MKYD QIVKSANAGK
	hIL-1RD8	EN.....ESGLC .YNSR..IRYL EKSEVTKRKE
	hFGR4	SLTSSNDDED PKSHRDPSNR HSYPQQAPYW THPQRMEKKL HAVPAGNTVK
50	mIL-1RD3	ITCPNVGDGYF P..SSVKPSVT WYKGCTEIVD FHN...VLPE GMNLSFFIPL
	hIL-1RD6	LTCHLHFPKS ...CVLGPIK WYKDCNEIKG E.....RFT VLETRLLVSN
	rIL-1RD6	LTCHLYFPES ...CVLDSIK WYKGCEEIKV S.....KKFC PTGTLVNN
	mIL-1RD4	ITCPPTIDLY.NWTAPVQ WFKNCALQE P.....RFR AHRSYLFIDN
55	hIL-1RD4	IYCPTIDLY.NWTAPLE WFKNCALQG S.....RYR AHKSFLVIDN
	hIL-1RD2	LVCndlSEFT R..DKTDVKIQ WYKDSLLLKD DNEK..FLSV RGTTHLLVHD
	mIL-1RD2	LVCndlKEFI S..SNADGKIQ WYKGAILLDK GNKE..FLSA GDPTRLLISN
	hIL-1RD10
	hIL-1RD5	ITCENSYYQ.TLVNSTS LYKNCKLKL ENN....KNP TIKKNAEF..
60	mIL-1RD5	ITCKNPNEY.ELIQDTW LYKNCKEISK TPRI...LKD AEFGDAEF..
	mIL-1RD1	LVCPLYSYFK DENNELPEVQ WYKNCKPLLL DN....VSFF GVKDPLLVRN
	hIL-1RD1	LVCPLYEFFK NENNELPKLQ WYKDCPKLLL DN....IHFS GVKDRLIVMN
	cIL-1RD1	IICPDLENFK DEDNINPEIH WYKECKSGFL EDKR..LVLA EGENAILILN
	hIL-1RD8	ISCPDMDDFK KSD.QEPDVW WYKECKPKMW R.....SIII QKGNAALLQE

	hFGR4	FRCPAAG... .NPTPTIR WLKDQAFHG ENRIGGIRLR HQHWSLVMES
	mIL-1RD3	VSNN.. GNYT CVVTYPENGR LFHLTRTVT KVVGS. PKDA LPPQIYSPND
5	hIL-1RD6	VSAEDRGNYA CQAILTHSGK QYEVLNGITV SITERAGYGG SVP. KIIYPK
	rIL-1RD6	IDVEDSGSYA CSARLTHLGR IFTVRNYIAV NTKE. VGSGG RIP. NITYPK
	mIL-1RD4	VTHDDEGDTY CQFTHAENGTY NYIVTATRSF TVE. EKGFS. MFPVITNPPY
	hIL-1RD4	VMTEDAGDTY CKFIHNENGA NYSVTATRSF TVKDEQGFS. LFPVIGAPAQ
	hIL-1RD2	VALEDAGYYR CVLTFAHCGQ QYNITRSEL RIKKK.. KEE TIPVIISP..
	mIL-1RD2	TSMDDAGYYR CVMTFTYNGQ EYNITRSEL RVKGT.. TTE PIPVIISP..
10	hIL-1RD10	... EFG.. TS CEL.. KYGGF V.. VRRTTEL TVTAPLTDKP PKLLYPMESK
	hIL-1RD5	... EDQGYYS CVHFLHHNGK LFNITKTFNII TIVED.. RSN IVPVLLGP.K
	mIL-1RD5	... GDEGYYS CVFSVHHNGT RYNITKTVNI TVIEG.. RSK VTPAILGP.K
	mIL-1RD1	VAEEHRGDYI CRMSYTFRGK QYPVIRVIQF ITIDE.. NKR DRPVILSP.R
	hIL-1RD1	VAEKHRGNYT CHASYTYLGK QYPITRVIEF ITLEE.. NKP TRPVIVSP.A
15	cIL-1RD1	VTIQDKGNYT CRMVYTYMGK QYNVSRTMNL EVKES.. PLK MRPEFIYP.N
	hIL-1RD8	VQEEDGGNYT CEL.. KYEGK L.. VRRTTEL KVTALLTDKP PKPLFFPMENQ
	hFGR4	VVPSDRGTYT CLVENAVGSI RYNYLLDVLE RSPH.. RPL QAGLPANTT.
	mIL-1RD3	RVVEYEKEPGE ELVIPCKVYF SFIMD.SHNE VVWTIDGKKP .DDVTVDITI
20	hIL-1RD6	NHSIEVQLGT TLIVDCNVTD TK.. D.NTNL RCWRVNNTLV DDYYDESKRI
	rIL-1RD6	NNSIEVQLGS TLIVDCNITD TK.. E.NTNL RCWRVNNTLV DDYYNDFKRI
	mIL-1RD4	NHTMEVEIGK PASIACSACF GKGSH.FLAD VLWQINKTVV GNFGEARIQE
	hIL-1RD4	NEIKEVEIGK NANLTCASACF GKGTQ.FLAA VLWQLNGTKI TDFGEPRIQQ
	hIL-1RD2	LKTISASLGS RLTIPCKVFL GTGTP.LTTM LWWTANDTHI .ESAYPGGRV
25	mIL-1RD2	LETIPASLGS RLIVPCKVFL GTGTS.SNTI VWWLANSTFI .SAAYPRGRV
	hIL-1RD10	LTIQETQLGD SANLTCRAFF GYSGD.VSPL IYWMKGEKFI EDLDENRVWE
	hIL-1RD5	LNVVAELGK NVRLNCSALL N.... EEDV IYWMFGEENG ... SDPNIHE
	mIL-1RD5	CEKVGVELGK DVELNCSASL N.... KDDL FYWSIRKEDS ... SDPNVQE
	mIL-1RD1	NETIEADPGS MIQLICNVTG Q.... FSDL VYWKWNGSEI .EWNDPFLAE
30	hIL-1RD1	NETMEVDLGS QIQLICNVTG Q.... LSDI AYWKWNGSVI .DEDDPVVLGE
	cIL-1RD1	NNTIEVELGS HHVMECNVSS GV.... YGLL PYWQVNDEDV .DSFDSTYRE
	hIL-1RD8	PSVIDVQLGK PLNIPCKAFF GFSGE.SGPM IYWMKGEKFI .EELAGHIRE
	hFGR4 AVVGS DVELLCKVYS DA... QPHIQ .. WLKHIVIN GSSFGA.. DG
	mIL-1RD3	NESVSYSSTE D.. ETRTQIL SIKKVTPEDL RRNYVCHARN TKGEAEQAAK
35	hIL-1RD6	REGVETHVSF REHNLYTVNI TFLEVKMEDY GLPFMCHAG. ... VSTAYII
	rIL-1RD6	QEGLTENLRL RNHILYTVNI TFLEVKMEDY GHPFTCHAA. ... VSAAYII
	mIL-1RD4	EEGRNESSSN D.MDCLTSVL RITGVTEKDL SLEYDCLALN LHGMIRHTIR
	hIL-1RD4	EEGQNQSFSN G.LACLDML RIADVKEEDL LLQYDCLALN LHGLRRHTVR
40	hIL-1RD2	TEGPRQEYSE NNENYIEVPL IFDPVTREDL HMDFKCVVHN TLSFQLRRTT
	mIL-1RD2	TEGLHHQYSE NDENYVEVSL IFDPVTREDL HTDFKCVASN PRSSQSLHTT
	hIL-1RD10	SDIRILKEHL G.EQEVSISL IVDSVEEGDL .GNYSCYVEN GNGRRHASVL
	hIL-1RD5	EKEMRIMTPE G.KWHASKVL RIENIGESNL NVLYNCTVAS TGGTDTSFI
	mIL-1RD5	DRKETTTWIS EGKLHASKIL RFQKITENYL NVLYNCTVAN EEAIDTKSFV
45	mIL-1RD1	DYQFVEHPST KRKYTLITTL NISEVKSQFY RYPFICVVKN TNIFESAHVQ
	hIL-1RD1	DYYSVENPAN KRRSTLITVL NISEIESRFY KHPFTCFAKN THGIDAAYIQ
	cIL-1RD1	QFYEEGMPHG .. IAVSGTKF NISEVKLKDY AYKFFCHFIY DSQEFTSYIK
	hIL-1RD8	GEIRLLKEHL G.EKEVELAL IFDSVVEADL AN.YTCHVEN RNRKHASVL
	hFGR4	FPYVQLKTA DINSEVEVL YLRNVAED. AGEYTCLAGN SIGLSYQSAW
50	mIL-1RD3	VKQKV.... I PPRYTVELAC GFGATVFLVV VLIVVV
	hIL-1RD6	LQLP.... A PDFRAYLIGG LIALVAVAVS VVYIYNIFKI DIVLWY
	rIL-1RD6	LKRP.... A PDFRAYLIGG LMAFLLLAVS ILIYIYNTFKV DIVLWY
	mIL-1RD4	LRRK.... Q PSKECPHIA IYYIVAGCSL LLMFINVLVI VL
55	hIL-1RD4	LSRK.... N PSKEC
	hIL-1RD2	VKEASS.... TFSWGIVLA PLSLAFLVLG GIWM
	mIL-1RD2	VKEVSS.... TFSWSIALA PLSLIILVVG AIW.
	hIL-1RD10	LHKREL.... MYTVELLAGG LGAILLLVC LVTIYKCY
	hIL-1RD5	LVRKADMADI P.. GHVFTRG MIIAVLILVA VVCLVTVCVI Y
60	mIL-1RD5	LVRKEIPDIP ... GHVFTGG VTVLVLASVA AVCIVILCVI Y
	mIL-1RD1	LIYP.... V PDFKNYLIGG FIILTATIVC CVCIIY
	hIL-1RD1	LIYP.... V TNFQKHMIGI CVTLTVIIVC SVFIY
	cIL-1RD1	LEHP.... V QNIRGYLIGG GISLIFLLFL ILIVY
	hIL-1RD8	LRKKDL.... IYKIELLAGG LGAIFLLVL LVVIYKCY

hFGR4 LTVLP....E EDPTWTAAAP EARYTDIILY ASGSLALAVL LLLAGLY..

Table 2

5

Alignment of the intracellular domains of various IL-1Rs. hIL-1RD9 is SEQ ID NO: 8; mIL-1RD9 is SEQ ID NO: 14; hIL-1RD1 is GenBank X16896; hIL-1RD6 is GenBank U49065; mIL-1RD3 is GenBank X85999; hIL-1RD8 is SEQ ID NO: 3; and mIL-1RD4 is GenBank Y07519.

10

	HuIL-1RD1	SDGKTYDAYI LYPKTVGEG.	STSDCDF VFKVLPEVLE KQCGYKLFYI
	HuIL-1RD6	VDGKLYDAYV LYPKPHKES.	QRHADAL VLNILPEVLE RQCGYKLFIF
	MoIL-1RD3	LDGKEYDIYV SYAR.	NVEEEEF VLLTLRGVLE NEFGYKLCIF
15	HuIL-1RD8	DDNKEYDAYL SYTKVDQDTL DCDNPEEEQF ALEVLPDVLE KHYGYKLFIP	
	HuIL-1RD5	TDGKTYDAFV SYLKECRP.	ENGEEHTF AVEILPRVLE KHFGYKLCIF
	MoIL-1RD9
	HuIL-1RD9
	MoIL-1RD4	NDGKLYDAYI IYPRVFRGS. AAGTHSVEYF VHHTLPDVLE NKCGYKLCIY	KGYSLCLL
20	HuIL-1RD1	GRDDYV.GED IVEVINENVK KSRRLLIIILV RETSGFSWLG GSSEEQIAMY	
	HuIL-1RD6	GRDEF.P.GQA VANVIDENVK LCRRLLIVIVV PESLGFGGLK NLSEEQIAVY	
	MoIL-1RD3	DRDSLPGGIV TDETLS.FIQ KSRRLLVVLS PNYVLQG.TQ ALLELKAGLE	
	HuIL-1RD8	ERDLIPSG.T YMEDLTRYVE QSRRLLIIVLT PDYILRR.GW SIFELESRLH	
25	HuIL-1RD5	ERDVVPGGAV VDEIHS.LIE KSRRLLIIVLS KSYMSN...E VRYELESGLH	
	MoIL-1RD9	DRDVTP.GGV YADDIVSIIK KSRRGIFILS PSYLN...P RVFELQAAVN	
	HuIL-1RD9	ERDVAP.GGV YAEDIVSIIK RSRRGIFILS PNYVNG...P SIFELQAAVN	
	MoIL-1RD4	GRDLLP.GQD AATVVESSIQ NSRRQVFVLA PHMMHSK..E FAYEQEIALH	
30	HuIL-1RD1	NALVQDGKIV VLLELEKIQ.	DYEKM PESIKFIKQK HGAIRWSGDF
	HuIL-1RD6	SALIQDGMKV ILIELEKIE.	DYTVM PESIQYIKQK HGAIRWHGDF
	MoIL-1RD3	NMASRGNINV ILVQYKAVK.	DMVKEL KRAKTVLT..
	HuIL-1RD8	NMLVSGEIKV ILIECTELKG KVNCQEVESEL KRSIKLLS..	VIWKGEK LIKWKGSK
	HuIL-1RD5	EALVERKIKI ILIEFTPVT.	DFTPL PQSLKLLKSH R.VLKWKADK
35	MoIL-1RD9	LALVDQTLKL ILIKFCFSQ.	EPESL PYLVKKALRV LPTVTWKGLK
	HuIL-1RD9	LALDDQTLKL ILIKFCYFQ.	EPESL PHLVKKALRV LPTVTWRGLK
	MoIL-1RD4	SALIQNNSKV ILIEMEPLG. EASRLQVGDL QDSLQHLVKI QGTIKWREDH	
40	HuIL-1RD1	TQGPQSAKTR FWKNVRYHMP VQRRSPSSKH	
	HuIL-1RD6	TEQSQCMKTK FWKTVRYHMP PRRCRPFLRS	
	MoIL-1RD3	SKYPQ...GR FWKQLQVAMP VKKSPRWSSN	
	HuIL-1RD8	SSKLN...SK FWKHLVYEMP IKKKEMLPRC	
	HuIL-1RD5	SLSYN...SR FWKNLLYLYMP AKTVKPGRDE	
	MoIL-1RD9	SVHAS...SR FWTQIRYHMP VKNSNRFMFN	
45	HuIL-1RD9	SVPPN...SR FWAKMRYHMP VKNSQGFTWN	
	MoIL-1RD4	VADKQSLSSK FWKHVRYQMP VPERASKTAS	

Table 3

50

Alignment of primate IL-1RD8 and primate IL-1RD10.

	RD8	MKPPFLLALV VCSVVSTNLK MVSKRNSVDG CIDWSVDLKT YMALAGEPVR
55	R1D0
	RD8	VKCALFYSYI RTNYSTAQST GLRLMWYKNK GDLEEPIIFS EVRMSKEEDS
	RD10
60	RD8	IWFHSAEAQD SGFYTCVLRN STYCMKVSMS LTVAENESGL CYNSRIRYLE
	RD10
	RD8	KSEVTKRKEI SCPDMDDFKK SDQEPDVVWY KECKPKMWRS IIIQKGNALL

	RD10
	RD8	IQEVAEEDGG NYTCELKYG KLVRRTEKLK VTALLTDKPP KPLFPMENQP
5	RD10EFG. .TSCELKYG FVVRRTTELT VTAPLTDKPP KLLYPMESKL
	RD8	SVIDVQLGKP LNIPCKAFFG FSGESGPMIY WMKGEKFIEE LAG.HIREGE
	RD10	TIQETQLGDS ANLTCRAFFG YSGDVSPLIY WMKGEKFIED LDENRVWESD
10	RD8	IRLLKEHLGE KEVELALIFD SVVEADLANY TCHVENRNGR KHASVLLRKK
	RD10	IRILKEHLGE QEVSISLIVD SVEEGDLGNY SCYVENGNGR RHASVLLHKR
	RD8	DLIYKIELAG GLGAIFLLLV LLVVIYKCYN IELMLFYRQH FGADETNDN
	RD10	ELMYTVELAG GLGAIFLLLV CLVTIYKCYK IEIMLFYRNH FGAEELDGDN
15	RD8	KEYDAYLSYT KVDQDTLDKD NPEEEQFALE VLPDVLEKHY GYKLFIPERD
	RD10	KDYDAYLSYT KVDPDQWNQE TGEEERFALE ILPDMLEKHY GYKLFIPDRD
20	RD8	LIPSGTYPED LTRYVEQSRR LIVLTPDYI LRRGWSIFEL ESRLHNMLVS
	RD10	LIPTGTYIED VARCVDQSKR LIVMTPNYV VRRGWSIFEL ETRLRNMLVT
	RD8	GEIKVILIEC TELKGKVNCQ EVESLKRSIK LLSLIKWKGS KSSKLNSKFW
	RD10	GEIKVILIEC SELRGIMNYQ EVEALKHTIK LLTVIKWHGP KCNKLNSKFW
25	RD8	KHLVYEMPIK KKEMLPRCHV LDSAEQGLFG ELQPIPSIAM TS.TSATLVS
	RD10	KRLQYEMPFK RIEPITHEQA LDVSEQGPFG ELQTVSAISM AAATSTALAT
	RD8	SQADLP.EFH PS..DSMQIR HCCRGYKHEI PAT.TLPVPS LGNHHTYCNL
	RD10	AHPDLRSTFH NTYHSQMRQK HYRSYEDV PPTGTLPLTS IGNQHTYCNI
30	RD8	PLTLLNGQLP LNNTLKD..T QEFHRNSSL PLSSKELSFT SDIW
	RD10	PMTLINGQRP QTKSSREQNP DEAHNTSAIL PLLPRETSIS SVIW

Table 4

Alignment and comparison of primate and rodent IL-1RD9.

Structural analysis of the primate IL-1RD10 sequence (SEQ ID NO: 18 and 20), in comparison with other IL-1Rs, shows characteristic features exist, which are conserved with the IL-1RD10 embodiment described herein. For 5 example, there are characteristic Ig domains, and subdomains therein. The corresponding regions of the IL-1RD10 (SEQ ID NO: 18 and 20) are about: f2 to gly7; g2 from val110 to thr23; a3 from leu30 to met33; a3' from thr38 to gln40; b3 from ala48 to ala54; c3 from pro64 to 10 lys70; c3' from glu72 to phe74; d3 from val83 to lys92; e3 from gln98 to val106; and f3 from tyr117 to trp126.

Structural analysis of the rodent IL-1RD9 sequence (SEQ ID NO: 12, 14, and 16), in comparison with other IL-1Rs, shows characteristic features exist (see Tables). 15 For example, there are characteristic Ig domains, and subdomains therein. The corresponding regions of the IL-1RD9 (SEQ ID NO: 12, 14, and 16) are about: Ig1 domain from gly18 to pro127, with cys105 probably linked to cys52 (or possibly cys48); Ig2 domain from gly128 to 20 pro229, with cys153 probably linked to cys199; and the Ig3 domain from glu230 to lys333, with cys251 probably linked to cys315; transmembrane segment from val336 to tyr360; THD domain from gly381 to val539; conserved trp residues probably correspond to residues 64, 169, and 25 267. Alignment of the IL-1RD9 embodiments is shown in Table 4. There are characteristic beta strand sections, and alpha helical structures, as described above for IL-1RD10. The corresponding segments of the human IL-1RD9 sequence (SEQ ID NO: 6, 8, and 10) are roughly: β_B from 30 gly3 to val13; α_2 from pro15 to lys28; β_C from ser30 to ser46; α_3 from ile47 to gln61; β_D from lys64 to glu75; α_4 from glu77 to leu87; β_E from val93 to leu98; and α_5 from arg106 to val117. The corresponding segments of the mouse IL-1RD9 sequence (SEQ ID NO: 12, 14, and 16) are 35 roughly: α_3 to gln10; β_D from lys13 to glu24; α_4 from glu26 to leu36; β_E from va42 to leu47; and α_5 from arg55 to val66.

As used herein, the terms IL-1 like receptor D8 (IL-1RD8), IL-1 like receptor D9 (IL-1RD9), or IL-1 like

receptor D10 (IL-1RD10) shall be used to describe a polypeptide comprising a segment having or sharing the amino acid sequence shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20, or a substantial fragment thereof.

5 The invention also includes a polypeptide variation of the respective IL-1RD8, IL-1RD9, IL-1RD10 alleles whose sequences are provided, e.g., a mutein or soluble extracellular or intracellular construct. Typically, such agonists or antagonists will exhibit less than about

10 10% sequence differences, and thus will often have between 1- and 11-fold substitutions, e.g., 2-, 3-, 5-, 7-fold, and others. It also encompasses allelic and other variants, e.g., natural polymorphic, of the polypeptide described. Typically, it will bind to its

15 corresponding biological ligand, perhaps in a dimerized state with an alpha receptor subunit, with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. The term shall

20 also be used herein to refer to related naturally occurring forms, e.g., alleles, polymorphic variants, and metabolic variants of the mammalian protein.

This invention also encompasses polypeptides having substantial amino acid sequence identity with the amino acid sequences shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20, preferably having segments of contiguous amino acid residues identical to segments of SEQ ID NO: 4, 10, or 20. It will include sequence variants with relatively few substitutions, e.g.,

25 typically less than about 25, ordinarily less than about 15, preferably less than about 3-5. Other embodiments include forms in association with an alpha subunit, e.g., an IL-1RD4, IL-1RD5, or IL-1RD6.

A substantial polypeptide "fragment", or "segment",

30 is a stretch of amino acid residues of at least about 8 contiguous amino acids, generally at least 10 contiguous amino acids, more generally at least 12 contiguous amino acids, often at least 14 contiguous amino acids, more often at least 16 contiguous amino acids, typically at

least 18 contiguous amino acids, more typically at least 20 contiguous amino acids, usually at least 22 contiguous amino acids, more usually at least 24 contiguous amino acids, preferably at least 26 contiguous amino acids,

5 more preferably at least 28 contiguous amino acids, and, in particularly preferred embodiments, at least about 30 or more contiguous amino acids, usually 40, 50, 70, 90, 110, etc. Sequences of segments of different polypeptides can be compared to one another over

10 appropriate length stretches. In many cases, the matching will involve a plurality of distinct, e.g., nonoverlapping, segments of the specified length. Typically, the plurality will be at least two, more usually at least three, and preferably 5, 7, or even

15 more. While the length minima are provided, longer lengths, of various sizes, may be appropriate, e.g., one of length 7, and two of length 12. Similar features apply to segments of nucleic acid.

Amino acid sequence homology, or sequence identity, 20 is determined by optimizing residue matches, if necessary, by introducing gaps as required. See, e.g., Needleham, et al. (1970) J. Mol. Biol. 48:443-453; Sankoff, et al. (1983) chapter one in Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group (GCG), Madison, WI; each of which is incorporated herein by reference. This changes when considering 30 conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and 35 phenylalanine, tyrosine. Homologous amino acid sequences are intended to include natural allelic and interspecies variations in the cytokine sequence. Typical homologous polypeptides will have from 50-100% homology (if gaps can be introduced), to 60-100% homology (if conservative

substitutions are included) with an amino acid sequence segment shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20. Homology measures will be at least about 70%, generally at least 76%, more generally at least 81%, 5 often at least 85%, more often at least 88%, typically at least 90%, more typically at least 92%, usually at least 94%, more usually at least 95%, preferably at least 96%, and more preferably at least 97%, and in particularly preferred embodiments, at least 98% or more. The degree 10 of homology will vary with the length of the compared segments. Homologous polypeptides, such as the allelic variants, will share most biological activities with the embodiments described in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20.

15 As used herein, the term "biological activity" is used to describe, without limitation, effects on inflammatory responses, innate immunity, and/or morphogenic development by respective ligands. For example, these receptors should, like IL-1 receptors, 20 mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et 25 al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738. Other activities include antigenic or immunogenic functions. The receptors exhibit biological 30 activities much like regulatable enzymes, regulated by ligand binding. However, the enzyme turnover number is more close to an enzyme than a receptor complex. Moreover, the numbers of occupied receptors necessary to induce such enzymatic activity is less than most receptor 35 systems, and may number closer to dozens per cell, in contrast to most receptors which will trigger at numbers in the thousands per cell. The receptors, or portions thereof, may be useful as phosphate labeling enzymes to label general or specific substrates.

The terms ligand, agonist, antagonist, and analog of, e.g., an IL-1RD8, IL-1RD9, or IL-1RD10, include molecules that modulate the characteristic cellular responses to IL-1 ligand proteins, as well as molecules 5 possessing the more standard structural binding competition features of ligand-receptor interactions, e.g., where the receptor is a natural receptor or an antibody. The cellular responses likely are mediated through binding of various IL-1 ligands to cellular 10 receptors related to, but possibly distinct from, the type I or type II IL-1 receptors. See, e.g., Belvin and Anderson (1996) Ann. Rev. Cell Dev. Biol. 12:393-416; Morisato and Anderson (1995) Ann. Rev. Genetics 29:371-3991 and Hultmark (1994) Nature 367:116-117.

15 Also, a ligand is a molecule which serves either as a natural ligand to which said receptor, or an analog thereof, binds, or a molecule which is a functional analog of the natural ligand. The functional analog may be a ligand with structural modifications, or may be a 20 wholly unrelated molecule which has a molecular shape which interacts with the appropriate ligand binding determinants. The ligands may serve as agonists or antagonists, see, e.g., Goodman, et al. (eds. 1990) Goodman & Gilman's: The Pharmacological Bases of 25 Therapeutics, Pergamon Press, New York.

Rational drug design may also be based upon structural studies of the molecular shapes of a receptor or antibody and other effectors or ligands. Effectors may be other proteins which mediate other functions in 30 response to ligand binding, or other proteins which normally interact with the receptor. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. 35 These will provide guidance as to which amino acid residues form molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein

Crystallography, Academic Press, New York, which is hereby incorporated herein by reference.

II. Activities

5 The IL-1 receptor-like polypeptides will have a number of different biological activities, e.g., in phosphate metabolism, being added to or removed from specific substrates, typically proteins. Such will generally result in modulation of an inflammatory 10 function, other innate immunity response, or a morphological effect. For example, a human IL-1RD9 gene coding sequence probably has about 60-80% identity with the nucleotide coding sequence of mouse IL-1RD9. At the 15 amino acid level, there is also likely to be reasonable identity.

The receptors will also exhibit immunogenic activity, e.g., in being capable of eliciting a selective immune response. Antiserum or antibodies resulting therefrom will exhibit both selectivity and affinity of 20 binding. The polypeptides will also be antigenic, in binding antibodies raised thereto, in the native state, or in denatured.

The biological activities of the IL-1RDs will generally be related to addition or removal of phosphate 25 moieties to substrates, typically in a specific manner, but occasionally in a non specific manner. Substrates may be identified, or conditions for enzymatic activity may be assayed by standard methods, e.g., as described in Hardie, et al. (eds. 1995) The Protein Kinase FactBook 30 vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 35 363:736-738.

III. Nucleic Acids

This invention contemplates use of isolated nucleic acid or fragments, e.g., which encode these or closely

related proteins, or fragments thereof, e.g., to encode a corresponding polypeptide, preferably one which is biologically active. In addition, this invention covers isolated or recombinant DNA which encodes such 5 polypeptides or polypeptides having characteristic sequences of the respective IL-1RDs, individually or as a group. Typically, the nucleic acid is capable of hybridizing, under appropriate conditions, with a nucleic acid coding sequence segment shown in SEQ ID NO: 1, 3, 5, 10 7, 9, 11, 13, 15, 17 or 19 but preferably not with a corresponding segment of other receptors. Said biologically active polypeptide can be a full length polypeptide, or fragment, and will typically have a 15 segment of amino acid sequence highly homologous to one shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20. Further, this invention covers the use of isolated or recombinant nucleic acid, or fragments thereof, which encode polypeptides having fragments which are equivalent to the IL-1RD9 proteins. The isolated nucleic acids can 20 have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others from the natural gene.

An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, or a mixed polymer, which is substantially 25 pure, e.g., separated from other components which naturally accompany a native sequence, e.g., ribosomes, polymerases, and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally 30 occurring environment, and includes recombinant or cloned DNA isolates, which are thereby distinguishable from naturally occurring compositions, and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. A substantially pure molecule 35 includes isolated forms of the molecule, either completely or substantially pure.

An isolated nucleic acid will generally be a homogeneous composition of molecules, but will, in some embodiments, contain heterogeneity, preferably minor.

This heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function or activity.

A "recombinant" nucleic acid is typically defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence. Typically this intervention involves in vitro manipulation, although under certain circumstances it may involve more classical animal breeding techniques. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants as found in their natural state. Thus, for example, products made by transforming cells with an unnaturally occurring vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such a process is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a restriction enzyme sequence recognition site. Alternatively, the process is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly available natural forms, e.g., encoding a fusion protein. Restriction enzyme recognition sites are often the target of such artificial manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. This will include a dimeric repeat. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode equivalent polypeptides to fragments of IL-1RD9 and fusions of

sequences from various different related molecules, e.g., other IL-1 receptor family members.

A "fragment" in a nucleic acid context is a contiguous segment of at least about 17 contiguous nucleotides, generally at least 21 contiguous nucleotides, more generally at least 25 contiguous nucleotides, ordinarily at least 30 contiguous nucleotides, more ordinarily at least 35 contiguous nucleotides, often at least 39 contiguous nucleotides, more often at least 45 contiguous nucleotides, typically at least 50 contiguous nucleotides, more typically at least 55 contiguous nucleotides, usually at least 60 contiguous nucleotides, more usually at least 66 contiguous nucleotides, preferably at least 72 contiguous nucleotides, more preferably at least 79 contiguous nucleotides, and in particularly preferred embodiments will be at least 85 or more contiguous nucleotides, e.g., 100, 120, 140, etc. Typically, fragments of different genetic sequences can be compared to one another over appropriate length stretches, particularly defined segments such as the domains described below.

A nucleic acid which codes for an IL-1RD8, IL-1RD9, or IL-1RD10 will be particularly useful to identify genes, mRNA, and cDNA species which code for itself or closely related proteins, as well as DNAs which code for polymorphic, allelic, or other genetic variants, e.g., from different individuals or related species. Preferred probes for such screens are those regions of the interleukin which are conserved between different polymorphic variants or which contain nucleotides which lack specificity, and will preferably be full length or nearly so. In other situations, polymorphic variant specific sequences will be more useful.

This invention further covers recombinant nucleic acid molecules and fragments having a nucleic acid sequence identical to or highly homologous to the isolated DNA set forth herein. In particular, the sequences will often be operably linked to DNA segments which control transcription, translation, and DNA

replication. These additional segments typically assist in expression of the desired nucleic acid segment.

Homologous, or highly identical, nucleic acid sequences, when compared to one another, e.g., IL-1RD9 sequences, exhibit significant similarity. The standards for homology in nucleic acids are either measures for homology generally used in the art by sequence comparison or based upon hybridization conditions. Comparative hybridization conditions are described in greater detail below.

Substantial identity in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 60% of the nucleotides, generally at least 66%, ordinarily at least 71%, often at least 76%, more often at least 80%, usually at least 84%, more usually at least 88%, typically at least 91%, more typically at least about 93%, preferably at least about 95%, more preferably at least about 96 to 98% or more, and in particular embodiments, as high as about 99% or more of the nucleotides, including, e.g., segments encoding structural domains such as the segments described below. Alternatively, substantial identity will exist when the segments will hybridize under selective hybridization conditions, to a strand or its complement, typically using a sequence derived from SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17 or 19. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, more typically at least about 65%, preferably at least about 75%, and more preferably at least about 90%. See, Kanehisa (1984) Nuc. Acids Res. 12:203-213, which is incorporated herein by reference. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, generally at least about 20 nucleotides, ordinarily at least about 24 nucleotides, usually at least about 28

nucleotides, typically at least about 32 nucleotides, more typically at least about 40 nucleotides, preferably at least about 50 nucleotides, and more preferably at least about 75 to 100 or more nucleotides.

5 Stringent conditions, in referring to homology in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters typically controlled in hybridization reactions. Stringent temperature conditions will usually
10 include temperatures in excess of about 30° C, more usually in excess of about 37° C, typically in excess of about 45° C, more typically in excess of about 55° C, preferably in excess of about 65° C, and more preferably in excess of about 70° C. Stringent salt conditions will
15 ordinarily be less than about 500 mM, usually less than about 400 mM, more usually less than about 300 mM, typically less than about 200 mM, preferably less than about 100 mM, and more preferably less than about 80 mM, even down to less than about 20 mM. However, the
20 combination of parameters is much more important than the measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370, which is hereby incorporated herein by reference. The signal should be at least 2X over background, generally at least 5-10X
25 over background, and preferably even more.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, 30 subsequent coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the
35 designated program parameters.

Optical alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2:482, by the homology alignment algorithm of Needleman and Wunsch

(1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman (1988) Proc. Nat'l Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the 5 Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (see generally Ausubel et al., *supra*).

One example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of 10 related sequences using progressive, pairwise alignments to show relationship and percent sequence identity. It also plots a tree or dendrogram showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of 15 Feng and Doolittle (1987) J. Mol. Evol. 35:351-360. The method used is similar to the method described by Higgins and Sharp (1989) CABIOS 5:151-153. The program can align up to 300 sequences, each of a maximum length of 5,000 nucleotides or amino acids. The multiple alignment 20 procedure begins with the pairwise alignment of the two most similar sequences, producing a cluster of two aligned sequences. This cluster is then aligned to the next most related sequence or cluster of aligned sequences. Two clusters of sequences are aligned by a 25 simple extension of the pairwise alignment of two individual sequences. The final alignment is achieved by a series of progressive, pairwise alignments. The program is run by designating specific sequences and their amino acid or nucleotide coordinates for regions of 30 sequence comparison and by designating the program parameters. For example, a reference sequence can be compared to other test sequences to determine the percent sequence identity relationship using the following 35 parameters: default gap weight (3.00), default gap length weight (0.10), and weighted end gaps.

Another example of algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described Altschul, et al. (1990) J. Mol. Biol. 215:403-410.

Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul, et al., *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a wordlength (W) of 11, the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Nat'l Acad. Sci. USA* 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul (1993) *Proc. Nat'l Acad. Sci. USA* 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than

about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

A further indication that two nucleic acid sequences of polypeptides are substantially identical is that the 5 polypeptide encoded by the first nucleic acid is immunologically cross reactive with the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, e.g., where the two peptides 10 differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules hybridize to each other under stringent conditions, as described below.

15 The isolated DNA can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode this polypeptide or its 20 derivatives. These modified sequences can be used to produce mutant proteins (muteins) or to enhance the expression of variant species. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant 25 IL-1RD9-like derivatives include predetermined or site-specific mutations of the polypeptide or its fragments, including silent mutations using genetic code degeneracy. "Mutant IL-1RD9" as used herein encompasses a polypeptide otherwise falling within the homology 30 definition of the IL-1R9 as set forth above, but having an amino acid sequence which differs from that of other IL-1RD-like polypeptides as found in nature, whether by way of deletion, substitution, or insertion. In particular, "site specific mutant IL-1RD9" encompasses a 35 polypeptide having substantial homology with a polypeptide of SEQ ID NO: 6, 8, 10, 12, 14 or 14, and typically shares most of the biological activities or effects of the forms disclosed herein.

Although site specific mutation sites are predetermined, mutants need not be site specific. Mammalian IL-1RD9 mutagenesis can be achieved by making amino acid insertions or deletions in the gene, coupled with expression. Substitutions, deletions, insertions, or many combinations may be generated to arrive at a final construct. Insertions include amino- or carboxy-terminal fusions. Random mutagenesis can be conducted at a target codon and the expressed mammalian IL-1RD9 mutants can then be screened for the desired activity, providing some aspect of a structure-activity relationship. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis. See also Sambrook, et al. (1989) and Ausubel, et al. (1987 and periodic Supplements).

The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce secondary mRNA structure such as loops or hairpins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Polymerase chain reaction (PCR) techniques can often be applied in mutagenesis. Alternatively, mutagenesis primers are commonly used methods for generating defined mutations at predetermined sites. See, e.g., Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA; and Dieffenbach and Dveksler (1995; eds.) PCR Primer: A Laboratory Manual Cold Spring Harbor Press, CSH, NY. Appropriate primers of length, e.g., 15, 20, 25, or longer can be made using sequence provided.

IV. Proteins, Peptides

As described above, the present invention encompasses primate IL-1RD8, primate or rodent IL-1RD9, 5 and primate IL-1RD10, e.g., whose sequences are disclosed e.g., in Tables 1-3, and described herein. Descriptions of features of IL-1RD9 are applicable in most cases, with appropriate modifications, also to IL-1RD8 and/or to IL-1RD10. Allelic and other variants are also contemplated, 10 including, e.g., fusion proteins combining portions of such sequences with others, including epitope tags and functional domains. Particularly interesting constructs will be intact extracellular or intracellular domains.

The present invention also provides recombinant 15 polypeptides, e.g., heterologous fusion proteins using segments from these rodent proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same manner. Thus, the fusion product of, e.g., an IL-1RD9 with 20 another IL-1 receptor is a continuous protein molecule having sequences fused in a typical polypeptide linkage, typically made as a single translation product and exhibiting properties, e.g., sequence or antigenicity, derived from each source peptide. A similar concept 25 applies to heterologous nucleic acid sequences.

In addition, new constructs may be made from combining similar functional or structural domains from other related proteins, e.g., IL-1 receptors or Toll-like receptors, including species variants. For example, 30 ligand-binding or other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992, each of which is incorporated herein by reference. Thus, 35 new chimeric polypeptides exhibiting new combinations of specificities will result from the functional linkage of receptor-binding specificities. For example, the ligand binding domains from other related receptor molecules may be added or substituted for other domains of this or

related proteins. The resulting protein will often have hybrid function and properties. For example, a fusion protein may include a targeting domain which may serve to provide sequestering of the fusion protein to a 5 particular subcellular organelle.

Candidate fusion partners and sequences can be selected from various sequence data bases, e.g., GenBank, c/o NCBI, and BCG, University of Wisconsin Biotechnology Computing Group, Madison, WI, which are each incorporated 10 herein by reference.

The present invention particularly provides muteins which bind IL-1-like ligands, and/or which are affected in signal transduction. Structural alignment of human IL-1RD9 with other members of the IL-1R family show 15 conserved features/residues. See Tables 1-4. Alignment of the human IL-1RD9 sequence with other members of the IL-1R family indicates various structural and functionally shared features. See also, Bazan, et al. (1996) Nature 379:591; Lodi, et al. (1994) Science 20:1762-1766; Sayle and Milner-White (1995) TIBS 20:374-376; and Gronenberg, et al. (1991) Protein Engineering 4:263-269.

The IL-1 α and IL-1 β ligands bind an IL-1 receptor type I (IL-1RD1) as the primary receptor and this complex 25 then forms a high affinity receptor complex with the IL-1 receptor type III (IL-1RD3). Such receptor subunits are probably shared with the receptors for the new IL-1 ligand family members. See, e.g., USSN 60/044,165 and USSN 60/055,111. It is likely that the IL-1 γ ligand 30 signals through a receptor comprising the association of IL-1RD9 (alpha component) with IL-1RD5 (beta component). The IL-1 δ and IL-1 ϵ ligands each probably signal through a receptor comprising the association of one of IL-1RD4, IL-1RD6, or IL-1RD9 (alpha components) with one of IL-35 1RD3, IL-1RD5, IL-1RD7, IL-1RD8, or IL-1RD10 (beta components).

Similar variations in other species counterparts of IL-1R sequences, e.g., receptors D1-D6, D8, D9, or D10, in the corresponding regions, should provide similar

interactions with ligand or substrate. Substitutions with either rodent or primate, e.g., mouse sequences or human sequences, are particularly preferred. Conversely, conservative substitutions away from the ligand binding 5 interaction regions will probably preserve most signaling activities; and conservative substitutions away from the intracellular domains will probably preserve most ligand binding properties.

"Derivatives" of the primate or mouse IL-1RD9 10 include amino acid sequence mutants, glycosylation variants, metabolic derivatives and covalent or aggregative conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of 15 functionalities to groups which are found in the IL-1RD9 amino acid side chains or at the N- or C- termini, e.g., by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or of residues containing carboxyl side chains, O-acyl derivatives of 20 hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g., lysine or arginine. Acyl groups are selected from the group of alkyl-moieties including C3 to C18 normal alkyl, thereby 25 forming alkanoyl aroyl species.

In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation 30 patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from cells which normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the 35 same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

A major group of derivatives are covalent conjugates of the receptors or fragments thereof with other polypeptides. These derivatives can be synthesized in recombinant culture such as N- or C-terminal fusions or 5 by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred derivatization sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

10 Fusion polypeptides between the receptors and other homologous or heterologous proteins are also provided. Homologous polypeptides may be fusions between different receptors, resulting in, for instance, a hybrid protein exhibiting binding specificity for multiple different IL- 15 1 ligands, or a receptor which may have broadened or weakened specificity of substrate effect. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. Typical examples are fusions of a 20 reporter polypeptide, e.g., luciferase, with a segment or domain of a receptor, e.g., a ligand-binding segment, so that the presence or location of a desired ligand may be easily determined. See, e.g., Dull, et al., U.S. Patent No. 4,859,609, which is hereby incorporated herein by 25 reference. Other gene fusion partners include glutathione-S-transferase (GST), bacterial β -galactosidase, trpE, Protein A, β -lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski, et al. (1988) Science 30 241:812-816.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by 35 synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Such polypeptides may also have amino acid residues which have been chemically modified by phosphorylation, sulfonation, biotinylation, or the addition or removal of other moieties, particularly those which have molecular 5 shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or serve as purification targets, e.g., affinity ligands.

Fusion proteins will typically be made by either recombinant nucleic acid methods or by synthetic 10 polypeptide methods. Techniques for nucleic acid manipulation and expression are described generally, e.g., in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), Vols. 1-3, Cold Spring Harbor Laboratory, and Ausubel, et al. (eds. 1987 and periodic 15 supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York, which are each incorporated herein by reference. Techniques for synthesis of polypeptides are described, e.g., in Merrifield (1963) J. Amer. Chem. Soc. 85:2149-2156; Merrifield (1986) Science 20 232: 341-347; and Atherton, et al. (1989) Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford; each of which is incorporated herein by reference. See also Dawson, et al. (1994) Science 266:776-779 for methods to make larger polypeptides.

25 This invention also contemplates the use of derivatives of an IL-1RD8, IL-1RD9, or IL-1RD10 other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives 30 generally fall into three classes: (1) salts, (2) side chain and terminal residue covalent modifications, and (3) adsorption complexes, for example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in 35 purification methods such as for affinity purification of a receptor or other binding molecule, e.g., an antibody. For example, an IL-1 ligand can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated Sepharose, by methods which are well

known in the art, or adsorbed onto polyolefin surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of an IL-1 receptor, antibodies, or other similar molecules. The ligand can 5 also be labeled with a detectable group, e.g., radioiodinated by the chloramine T procedure, covalently bound to rare earth chelates, or conjugated to another fluorescent moiety for use in diagnostic assays.

An IL-1RD8, IL-1RD9, or IL-1RD10 of this invention 10 can be used as an immunogen for the production of antisera or antibodies specific, e.g., capable of distinguishing between other IL-1 receptor family members, for the IL-1RD8, IL-1RD9, or IL-1RD10 or various fragments thereof. The purified IL-1RD8, IL-1RD9, or IL-15 1RD10 can be used to screen monoclonal antibodies or antigen-binding fragments prepared by immunization with various forms of impure preparations containing the protein. In particular, the term "antibodies" also encompasses antigen binding fragments of natural 20 antibodies, e.g., Fab, Fab2, Fv, etc. The purified IL-1RD9 can also be used as a reagent to detect antibodies generated in response to the presence of elevated levels of expression, or immunological disorders which lead to antibody production to the endogenous receptor.

25 Additionally, IL-1RD8, IL-1RD9, or IL-1RD10 fragments may also serve as immunogens to produce the antibodies of the present invention, as described immediately below. For example, this invention contemplates antibodies having binding affinity to or being raised against the amino 30 acid sequences shown, e.g., in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20, fragments thereof, or various homologous peptides. In particular, this invention contemplates antibodies having binding affinity to, or having been raised against, specific fragments which are 35 predicted to be, or actually are, exposed at the exterior polypeptide surface of the native IL-1RD8, IL-1RD9, or IL-1RD10. Various preparations of desired selectivity in binding can be prepared by appropriate cross absorptions, etc.

The blocking of physiological response to the receptor ligands may result from the inhibition of binding of the ligand to the receptor, likely through competitive inhibition. Thus, in vitro assays of the 5 present invention will often use antibodies or antigen binding segments of these antibodies, or fragments attached to solid phase substrates. These assays will also allow for the diagnostic determination of the 10 effects of either ligand binding region mutations and modifications, or other mutations and modifications, e.g., which affect signaling or enzymatic function.

This invention also contemplates the use of competitive drug screening assays, e.g., where neutralizing antibodies to the receptor or fragments 15 compete with a test compound for binding to a ligand or other antibody. In this manner, the neutralizing antibodies or fragments can be used to detect the presence of a polypeptide which shares one or more binding sites to a receptor and can also be used to 20 occupy binding sites on a receptor that might otherwise bind a ligand.

V. Making Nucleic Acids and Protein

DNA which encodes the polypeptides or fragments 25 thereof can be obtained by chemical synthesis, screening cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples. Natural sequences can be isolated using standard methods and the sequences provided herein, e.g., 30 in Tables 1-3. Other species counterparts can be identified by hybridization techniques, or by various PCR techniques, combined with or by searching in sequence databases, e.g., GenBank.

This DNA can be expressed in a wide variety of host 35 cells for the synthesis of a full-length receptor or fragments which can in turn, e.g., be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified ligand binding or kinase/phosphatase domains; and for

structure/function studies. Variants or fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. These molecules can be substantially free of protein or 5 cellular contaminants, other than those derived from the recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable carrier and/or diluent. The protein, or portions thereof, may be expressed as fusions 10 with other proteins.

Expression vectors are typically self-replicating DNA or RNA constructs containing the desired receptor gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in 15 a suitable host cell. These control elements are capable of effecting expression within a suitable host. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a 20 prokaryotic promoter system or a eukaryotic promoter expression control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that 25 encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that allows the vector to replicate independently of the host cell.

30 The vectors of this invention include those which contain DNA which encodes a protein, as described, or a fragment thereof encoding a biologically active equivalent polypeptide. The DNA can be under the control of a viral promoter and can encode a selection marker.

35 This invention further contemplates use of such expression vectors which are capable of expressing eukaryotic cDNA coding for such a polypeptide in a prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNA

coding for the receptor is inserted into the vector such that growth of the host containing the vector expresses the cDNA in question. Usually, expression vectors are designed for stable replication in their host cells or

5 for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell, e.g., it is possible to effect transient expression of the polypeptide or its fragments in various

10 hosts using vectors that do not contain a replication origin that is recognized by the host cell. It is also possible to use vectors that cause integration of the polypeptide encoding portion or its fragments into the host DNA by recombination.

15 Vectors, as used herein, comprise plasmids, viruses, bacteriophage, integratable DNA fragments, and other vehicles which enable the integration of DNA fragments into the genome of the host. Expression vectors are specialized vectors which contain genetic control

20 elements that effect expression of operably linked genes. Plasmids are the most commonly used form of vector but all other forms of vectors which serve an equivalent function and which are, or become, known in the art are suitable for use herein. See, e.g., Pouwels, et al.

25 (1985 and Supplements) Cloning Vectors: A Laboratory Manual, Elsevier, N.Y., and Rodriguez, et al. (eds.) Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Butterworth, Boston, 1988, which are incorporated herein by reference.

30 Transformed cells are cells, preferably mammalian, that have been transformed or transfected with receptor vectors constructed using recombinant DNA techniques. Transformed host cells usually express the desired polypeptide or its fragments, but for purposes of

35 cloning, amplifying, and manipulating its DNA, do not need to express the subject protein. This invention further contemplates culturing transformed cells in a nutrient medium, thus permitting the receptor to accumulate in the cell membrane. The polypeptide can be

recovered, either from the culture or, in certain instances, from the culture medium.

For purposes of this invention, nucleic sequences are operably linked when they are functionally related to each other. For example, DNA for a presequence or secretory leader is operably linked to a polypeptide if it is expressed as a preprotein or participates in directing the polypeptide to the cell membrane or in secretion of the polypeptide. A promoter is operably linked to a coding sequence if it controls the transcription of the polypeptide; a ribosome binding site is operably linked to a coding sequence if it is positioned to permit translation. Usually, operably linked means contiguous and in reading frame, however, certain genetic elements such as repressor genes are not contiguously linked but still bind to operator sequences that in turn control expression.

Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., E. coli and B. subtilis. Lower eukaryotes include yeasts, e.g., S. cerevisiae and Pichia, and species of the genus Dictyostelium. Higher eukaryotes include established tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents.

Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, E. coli and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or many of its derivatives. Vectors that can be used to express the receptor or its fragments include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius, et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in

Vectors: A Survey of Molecular Cloning Vectors and Their Uses, (eds. Rodriguez and Denhardt), Butterworth, Boston, Chapter 10, pp. 205-236, which is incorporated herein by reference.

5 Lower eukaryotes, e.g., yeasts and Dictyostelium, may be transformed with IL-1RD9 sequence containing vectors. For purposes of this invention, the most common lower eukaryotic host is the baker's yeast, Saccharomyces cerevisiae. It will be used to generically represent
10 lower eukaryotes although a number of other strains and species are also available. Yeast vectors typically consist of a replication origin (unless of the integrating type), a selection gene, a promoter, DNA encoding the receptor or its fragments, and sequences for
15 translation termination, polyadenylation, and transcription termination. Suitable expression vectors for yeast include such constitutive promoters as 3-phosphoglycerate kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the
20 alcohol dehydrogenase 2 promoter or metallothioneine promoter. Suitable vectors include derivatives of the following types: self-replicating low copy number (such as the YRp-series), self-replicating high copy number (such as the YEp-series); integrating types (such as the
25 YIp-series), or mini-chromosomes (such as the YCp-series).

Higher eukaryotic tissue culture cells are normally the preferred host cells for expression of the functionally active interleukin protein. In principle, 30 many higher eukaryotic tissue culture cell lines are workable, e.g., insect baculovirus expression systems, whether from an invertebrate or vertebrate source. However, mammalian cells are preferred. Transformation or transfection and propagation of such cells has become
35 a routine procedure. Examples of useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell lines, baby rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines. Expression vectors for such cell lines usually include an

origin of replication, a promoter, a translation initiation site, RNA splice sites (if genomic DNA is used), a polyadenylation site, and a transcription termination site. These vectors also usually contain a 5 selection gene or amplification gene. Suitable expression vectors may be plasmids, viruses, or retroviruses carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of 10 suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo PolyA, see Thomas, et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610.

For secreted proteins, an open reading frame usually 15 encodes a polypeptide that consists of a mature or secreted product covalently linked at its N-terminus to a signal peptide. The signal peptide is cleaved prior to secretion of the mature, or active, polypeptide. The cleavage site can be predicted with a high degree of 20 accuracy from empirical rules, e.g., von-Heijne (1986) Nucleic Acids Research 14:4683-4690 and Nielsen, et al. (1997) Protein Eng. 10:1-12, and the precise amino acid composition of the signal peptide often does not appear to be critical to its function, e.g., Randall, et al. 25 (1989) Science 243:1156-1159; Kaiser, et al. (1987) Science 235:312-317.

It will often be desired to express these 30 polypeptides in a system which provides a specific or defined glycosylation pattern. In this case, the usual pattern will be that provided naturally by the expression system. However, the pattern will be modifiable by exposing the polypeptide, e.g., an unglycosylated form, to appropriate glycosylating proteins introduced into a heterologous expression system. For example, the 35 receptor gene may be co-transformed with one or more genes encoding mammalian or other glycosylating enzymes. Using this approach, certain mammalian glycosylation patterns will be achievable in prokaryote or other cells.

The source of IL-1RD8, IL-1RD9, or IL-1RD10 can be a eukaryotic or prokaryotic host expressing recombinant IL-1RD8, IL-1RD9, or IL-1RD10 such as is described above. The source can also be a cell line such as mouse Swiss 5 3T3 fibroblasts, but other mammalian cell lines are also contemplated by this invention, with the preferred cell line being from the human species.

Now that the sequences are known, the primate IL-1Rs, fragments, or derivatives thereof can be prepared by 10 conventional processes for synthesizing peptides. These include processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis, 15 Springer-Verlag, New York; and Bodanszky (1984) The Principles of Peptide Synthesis, Springer-Verlag, New York; all of each which are incorporated herein by reference. For example, an azide process, an acid chloride process, an acid anhydride process, a mixed 20 anhydride process, an active ester process (e.g., p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimidazole process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD) /additive process can be 25 used. Solid phase and solution phase syntheses are both applicable to the foregoing processes. Similar techniques can be used with partial IL-1RD9 sequences.

The IL-1RD8, IL-1RD9, or IL-1RD10 proteins, polypeptides, fragments, or derivatives are suitably 30 prepared in accordance with the above processes as typically employed in peptide synthesis, generally either by a so-called stepwise process which comprises condensing an amino acid to the terminal amino acid, one by one in sequence, or by coupling peptide fragments to 35 the terminal amino acid. Amino groups that are not being used in the coupling reaction typically must be protected to prevent coupling at an incorrect location.

If a solid phase synthesis is adopted, the C-terminal amino acid is bound to an insoluble carrier or

support through its carboxyl group. The insoluble carrier is not particularly limited as long as it has a binding capability to a reactive carboxyl group.

5 Examples of such insoluble carriers include halomethyl resins, such as chloromethyl resin or bromomethyl resin, hydroxymethyl resins, phenol resins, tert-alkyloxycarbonylhydrazidated resins, and the like.

An amino group-protected amino acid is bound in sequence through condensation of its activated carboxyl 10 group and the reactive amino group of the previously formed peptide or chain, to synthesize the peptide step by step. After synthesizing the complete sequence, the peptide is split off from the insoluble carrier to produce the peptide. This solid-phase approach is 15 generally described by Merrifield, et al. (1963) in J. Am. Chem. Soc. 85:2149-2156, which is incorporated herein by reference.

The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means 20 of peptide separation, e.g., by extraction, precipitation, electrophoresis, various forms of chromatography, and the like. The receptors of this invention can be obtained in varying degrees of purity depending upon desired uses. Purification can be 25 accomplished by use of the protein purification techniques disclosed herein, see below, or by the use of the antibodies herein described in methods of immunoabsorbant affinity chromatography. This immunoabsorbant affinity chromatography is carried out by 30 first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized lysates of appropriate cells, lysates of other cells expressing the receptor, or lysates or supernatants of cells producing the polypeptide as a result of DNA techniques, 35 see below.

Generally, the purified protein will be at least about 40% pure, ordinarily at least about 50% pure, usually at least about 60% pure, typically at least about 70% pure, more typically at least about 80% pure,

preferable at least about 90% pure and more preferably at least about 95% pure, and in particular embodiments, 97%-99% or more. Purity will usually be on a weight basis, but can also be on a molar basis. Different assays will 5 be applied as appropriate. Similar concepts apply to polynucleotides and antibodies.

VI. Antibodies

Antibodies can be raised to the various mammalian 10 IL-1RD8, IL-1RD9, or IL-1RD10 described herein, e.g.; primate IL-1RD9 polypeptides and fragments thereof, both in naturally occurring native forms and in their recombinant forms, the difference being that antibodies to the active receptor are more likely to recognize 15 epitopes which are only present in the native conformations. Denatured antigen detection can also be useful in, e.g., Western analysis. Anti-idiotypic antibodies are also contemplated, which would be useful as agonists or antagonists of a natural receptor or an 20 antibody.

Antibodies, including binding fragments and single chain versions, against predetermined fragments of the polypeptide can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins. 25 Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies can be screened for binding to normal or defective protein, or screened for agonistic or antagonistic activity. These monoclonal antibodies will usually bind with at least a K_D of about 30 1 mM, more usually at least about 300 μ M, typically at least about 100 μ M, more typically at least about 30 μ M, preferably at least about 10 μ M, and more preferably at least about 3 μ M or better.

The antibodies, including antigen binding fragments, 35 of this invention can have significant diagnostic or therapeutic value. They can be potent antagonists that bind to the receptor and inhibit binding to ligand or inhibit the ability of the receptor to elicit a biological response, e.g., act on its substrate. They

also can be useful as non-neutralizing antibodies and can be coupled to toxins or radionuclides to bind producing cells, or cells localized to the source of the interleukin. Further, these antibodies can be conjugated 5 to drugs or other therapeutic agents, either directly or indirectly by means of a linker.

The antibodies of this invention can also be useful in diagnostic applications. As capture or non-neutralizing antibodies, they might bind to the 10 receptor without inhibiting ligand or substrate binding. As neutralizing antibodies, they can be useful in competitive binding assays. They will also be useful in detecting or quantifying ligand. They may be used as reagents for Western blot analysis, or for 15 immunoprecipitation or immunopurification of the respective protein.

Protein fragments may be joined to other materials, particularly polypeptides, as fused or covalently joined polypeptides to be used as immunogens. Mammalian IL-1Rs 20 and fragments may be fused or covalently linked to a variety of immunogens, such as keyhole limpet hemocyanin, bovine serum albumin, tetanus toxoid, etc. See Microbiology, Hoeber Medical Division, Harper and Row, 1969; Landsteiner (1962) Specificity of Serological 25 Reactions, Dover Publications, New York; and Williams, et al. (1967) Methods in Immunology and Immunochemistry, Vol. 1, Academic Press, New York; each of which are incorporated herein by reference, for descriptions of methods of preparing polyclonal antisera. A typical 30 method involves hyperimmunization of an animal with an antigen. The blood of the animal is then collected shortly after the repeated immunizations and the gamma globulin is isolated.

In some instances, it is desirable to prepare 35 monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.), Lange Medical

Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed.) Academic Press, New York; and particularly in Kohler and Milstein (1975) in Nature 256:495-497, which discusses one method of generating monoclonal antibodies. Each of these references is incorporated herein by reference.

Summarized briefly, this method involves injecting an animal with an immunogen. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing in vitro. The population of hybridomas is then screened to isolate individual clones, each of which secrete a single antibody species to the immunogen. In this manner, the individual antibody species obtained are the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic substance.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors. See, Huse, et al. (1989) "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546, each of which is hereby incorporated herein by reference. The polypeptides and antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent

moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant or chimeric 5 immunoglobulins may be produced, see Cabilly, U.S. Patent No. 4,816,567; or made in transgenic mice, see Mendez, et al. (1997) Nature Genetics 15:146-156. These references are incorporated herein by reference.

The antibodies of this invention can also be used 10 for affinity chromatography in isolating the IL-1Rs. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, Sephadex, or the like, where a cell lysate may be passed through the column, the column washed, followed by 15 increasing concentrations of a mild denaturant, whereby the purified protein will be released. The protein may be used to purify antibody.

The antibodies may also be used to screen expression 20 libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled with a moiety allowing easy detection of presence of antigen by antibody binding.

Antibodies raised against an IL-1R will also be used 25 to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the protein or cells which express the protein. They also will be useful as agonists or antagonists of the ligand, which may be competitive inhibitors or substitutes for naturally 30 occurring ligands.

An IL-1R polypeptide that specifically binds to or 35 that is specifically immunoreactive with an antibody generated against a defined immunogen, such as an immunogen consisting of the amino acid sequence of, e.g., SEQ ID NO: 4, 10, or 20, is typically determined in an immunoassay. The immunoassay typically uses a polyclonal antiserum which was raised, e.g., to a polypeptide of SEQ ID NO: 4, 10, or 20. This antiserum is selected to have low crossreactivity against other IL-1R family members,

e.g., IL-1Rs D1 through D8, preferably from the same species, and any such crossreactivity is removed by immunoabsorption prior to use in the immunoassay.

To produce antisera for use in an immunoassay, the 5 polypeptide of, e.g., SEQ ID NO: 4, 10, or 20, is isolated as described herein. For example, recombinant polypeptide may be produced in a mammalian cell line. An appropriate host, e.g., an inbred strain of mice such as Balb/c, is immunized with the selected protein, typically 10 using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, *supra*). Alternatively, a synthetic peptide derived from the sequences disclosed herein and conjugated to a carrier polypeptide can be used an immunogen. Polyclonal 15 sera are collected and titered against the immunogen polypeptide in an immunoassay, e.g., a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross 20 reactivity against other IL-1R family members, e.g., IL-1RD1 through IL-1RD6, using a competitive binding immunoassay such as the one described in Harlow and Lane, *supra*, at pages 570-573. Preferably at least two IL-1R family members are used in this determination. These IL- 25 1R family members can be produced as recombinant polypeptides and isolated using standard molecular biology and protein chemistry techniques as described herein.

30 Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example, the polypeptide of SEQ ID NO: 4, 10, or 20 can be immobilized to a solid support. Polypeptides added to the assay compete with the binding of the antisera to the immobilized antigen. The ability of the above 35 polypeptides to compete with the binding of the antisera to the immobilized polypeptide is compared to the polypeptides of IL-1RD1 through IL-1RD6. The percent crossreactivity for the above polypeptides is calculated, using standard calculations. Those antisera with less

than 10% crossreactivity with each of the polypeptides listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption with the above-listed proteins.

5 The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second polypeptide to the immunogen polypeptide (e.g., the IL-1RD8, IL-1RD9, or IL-1RD10 like polypeptide of SEQ ID NO: 4, 10, or 20). To make this
10 comparison, the two polypeptides are each assayed at a wide range of concentrations and the amount of each polypeptide required to inhibit 50% of the binding of the antisera to the immobilized polypeptide is determined. If the amount of the second polypeptide required is less
15 than twice the amount of the polypeptide of the selected polypeptide or polypeptides that is required, then the second polypeptide is said to specifically bind to an antibody generated to the immunogen.

It is understood that these IL-1R polypeptides are
20 members of a family of homologous polypeptides that comprise at least 7 genes previously identified. For a particular gene product, such as, e.g., IL-1RD9, the term refers not only to the amino acid sequences disclosed herein, but also to other polypeptides that are allelic,
25 non-allelic, or species variants. It is also understood that the terms include nonnatural mutations introduced by deliberate mutation using conventional recombinant technology such as single site mutation, or by excising short sections of DNA encoding the respective proteins,
30 or by substituting new amino acids, or adding new amino acids. Such minor alterations typically will substantially maintain the immunoidentity of the original molecule and/or its biological activity. Thus, these alterations include polypeptides that are specifically
35 immunoreactive with a designated naturally occurring IL-1RD8, IL-1RD9, or IL-1RD10 protein. The biological properties of the altered polypeptides can be determined by expressing the polypeptide in an appropriate cell line and measuring the appropriate effect, e.g., upon

transfected lymphocytes. Particular polypeptide modifications considered minor would include conservative substitution of amino acids with similar chemical properties, as described above for the IL-1R family as a whole. By aligning a polypeptide optimally with the polypeptide of the IL-1Rs and by using the conventional immunoassays described herein to determine immunoidentity, one can determine the polypeptide compositions of the invention.

10

VII. Kits and quantitation

Both naturally occurring and recombinant forms of the IL-1R like molecules of this invention are particularly useful in kits and assay methods. For example, these methods would also be applied to screening for binding activity, e.g., ligands for these proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds per year. See, e.g., a BIOMEK automated workstation, Beckman Instruments, Palo Alto, California, and Fodor, et al. (1991) Science 251:767-773, which is incorporated herein by reference. The latter describes means for testing binding by a plurality of defined polymers synthesized on a solid substrate. The development of suitable assays to screen for a ligand or agonist/antagonist homologous polypeptides can be greatly facilitated by the availability of large amounts of purified, soluble IL-1Rs in an active state such as is provided by this invention.

30

Purified IL-1RD8, IL-1RD9, or IL-1RD10 can be coated directly onto plates for use in the aforementioned ligand screening techniques. However, non-neutralizing antibodies to these polypeptides can be used as capture antibodies to immobilize the respective receptor on the solid phase, useful, e.g., in diagnostic uses.

This invention also contemplates use of IL-1RD8, IL-1RD9, or IL-1RD10 fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting the presence of the protein or its

ligand. Alternatively, or additionally, antibodies against the molecules may be incorporated into the kits and methods. Typically the kit will have a compartment containing, e.g., either an IL-1RD9 peptide or gene 5 segment or a reagent which recognizes one or the other. Typically, recognition reagents, in the case of peptide, would be a ligand or antibody, or in the case of a gene segment, would usually be a hybridization probe.

A preferred kit for determining the concentration of 10 IL-1RD8, IL-1RD9, or IL-1RD10 in a sample would typically comprise a labeled compound, e.g., ligand or antibody, having known binding affinity for IL-1RD9, a source of IL-1RD9 (naturally occurring or recombinant) as a positive control, and a means for separating the bound 15 from free labeled compound, for example a solid phase for immobilizing the IL-1RD9 in the test sample. Compartments containing reagents, and instructions, will normally be provided.

Antibodies, including antigen binding fragments, 20 specific for mammalian IL-1RD8 or a peptide fragment, or receptor fragments are useful in diagnostic applications to detect the presence of elevated levels of ligand and/or its fragments. Diagnostic assays may be homogeneous (without a separation step between free 25 reagent and antibody-antigen complex) or heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), 30 substrate-labeled fluorescent immunoassay (SLFIA) and the like. For example, unlabeled antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to an IL-1R or to a particular fragment thereof. These assays have also been 35 extensively discussed in the literature. See, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH., and Coligan (ed. 1991) and periodic supplements, Current Protocols In Immunology Greene/Wiley, New York.

Anti-idiotypic antibodies may have similar use to serve as agonists or antagonists of IL-1Rs. These should be useful as therapeutic reagents under appropriate circumstances.

5 Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay, the protocol, and the label, either labeled or unlabeled antibody, or labeled ligand is
10 provided. This is usually in conjunction with other additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the
15 contents after use. Typically the kit has compartments for each useful reagent, and will contain instructions for proper use and disposal of reagents. Desirably, the reagents are provided as a dry lyophilized powder, where the reagents may be reconstituted in an aqueous medium
20 having appropriate concentrations for performing the assay.

The aforementioned constituents of the diagnostic assays may be used without modification or may be modified in a variety of ways. For example, labeling may
25 be achieved by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In many of these assays, a test compound, IL-1R, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include
30 label groups: radiolabels such as ^{125}I , enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence
35 polarization. Both of the patents are incorporated herein by reference. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free ligand, or alternatively the bound from the free test compound. The IL-1R can be immobilized on various matrixes followed by washing.

5 Suitable matrices include plastic such as an ELISA plate, filters, and beads. Methods of immobilizing the receptor to a matrix include, without limitation, direct adhesion to plastic, use of a capture antibody, chemical coupling, and biotin-avidin. The last step in this approach
10 involves the precipitation of antibody/antigen complex by any of several methods including those utilizing, e.g., an organic solvent such as polyethylene glycol or a salt such as ammonium sulfate. Other suitable separation techniques include, without limitation, the fluorescein
15 antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30(9):1457-1461, and the double antibody magnetic particle separation as described in U.S. Pat. No. 4,659,678, each of which is incorporated herein by reference.

20 The methods for linking protein or fragments to various labels have been extensively reported in the literature and do not require detailed discussion here. Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or
25 active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group with an activated halogen such as chloroacetyl, or an activated olefin such as maleimide, for linkage, or the like. Fusion polypeptides will also find use in these
30 applications.

Another diagnostic aspect of this invention involves use of oligonucleotide or polynucleotide sequences taken from the sequence of an IL-1R. These sequences can be used as probes for detecting levels of the respective IL-35 1R in patients suspected of having an immunological disorder. The preparation of both RNA and DNA nucleotide sequences, the labeling of the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. Normally

an oligonucleotide probe should have at least about 14 nucleotides, usually at least about 18 nucleotides, and the polynucleotide probes may be up to several kilobases. Various labels may be employed, most commonly

5 radionuclides, particularly ^{32}P . However, other techniques may also be employed, such as using biotin modified nucleotides for introduction into a polynucleotide. The biotin then serves as the site for binding to avidin or antibodies, which may be labeled

10 with a wide variety of labels, such as radionuclides, fluorescers, enzymes, or the like. Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes, or DNA-protein duplexes. The antibodies

15 in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected. The use of probes to the novel anti-sense RNA may be carried out in

20 conventional techniques such as nucleic acid hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). This also includes amplification techniques such as polymerase chain

25 reaction (PCR).

Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the combination of multiple indications used as markers.

30 Thus, kits may test for combinations of markers. See, e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97.

VIII. Therapeutic Utility

35 This invention provides reagents with significant therapeutic value. The IL-1Rs (naturally occurring or recombinant), fragments thereof, mutein receptors, and antibodies, along with compounds identified as having binding affinity to the receptors or antibodies, should

be useful in the treatment of conditions exhibiting abnormal expression of the receptors of their ligands. Such abnormality will typically be manifested by immunological disorders. Additionally, this invention 5 should provide therapeutic value in various diseases or disorders associated with abnormal expression or abnormal triggering of response to the ligand. The IL-1 ligands have been suggested to be involved in morphologic development, e.g., dorso-ventral polarity determination, 10 and immune responses, particularly the primitive innate responses. See, e.g., Sun, et al. (1991) Eur. J. Biochem. 196:247-254; Hultmark (1994) Nature 367:116-117.

Recombinant IL-1Rs, muteins, agonist or antagonist antibodies thereto, or antibodies can be purified and 15 then administered to a patient. These reagents can be combined for therapeutic use with additional active ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, along with physiologically innocuous stabilizers and excipients. 20 These combinations can be sterile, e.g., filtered, and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This invention also contemplates use of antibodies or binding fragments thereof which are not complement 25 binding.

Ligand screening using IL-1R or fragments thereof can be performed to identify molecules having binding affinity to the receptors. Subsequent biological assays can then be utilized to determine if a putative ligand 30 can provide competitive binding, which can block intrinsic stimulating activity. Receptor fragments can be used as a blocker or antagonist in that it blocks the activity of ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor 35 and is thus an agonist in that it simulates the activity of ligand, e.g., inducing signaling. This invention further contemplates the therapeutic use of antibodies to IL-1Rs as antagonists.

The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, reagent physiological life, pharmacological life, physiological state of the patient, and other medicants administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used *in vitro* may provide useful guidance in the amounts useful for *in situ* administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds., 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; each of which is hereby incorporated herein by reference. Methods for administration are discussed therein and below, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, New Jersey. Because of the likely high affinity binding, or turnover numbers, between a putative ligand and its receptors, low dosages of these reagents would be initially expected to be effective. And the signaling pathway suggests extremely low amounts of ligand may have effect. Thus, dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μ M concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or slow release apparatus will often be utilized for continuous administration.

IL-1Rs, fragments thereof, and antibodies or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the

size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many conventional 5 dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations comprise at least one active ingredient, as defined above, together with one or more acceptable carriers 10 thereof. Each carrier must be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including 15 subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds. 1990) Goodman and Gilman's: The 20 Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; Avis, et al. (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, et al. (eds. 1990) 25 Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention may be combined with or used in association with other therapeutic agents, particularly agonists or 30 antagonists of other IL-1 family members.

IX. Ligands

The description of the IL-1 receptors herein provide means to identify ligands, as described above. Such 35 ligand should bind specifically to the respective receptor with reasonably high affinity. Typical ligand receptor binding constants will be at least about 30 mM, e.g., generally at least about 3 mM, more generally at least about 300 μ M, typically at least about 30 μ M, 3 μ M, 40 300 nM, 30 nM, etc. Various constructs are made

available which allow either labeling of the receptor to detect its ligand. For example, directly labeling IL-1R, fusing onto it markers for secondary labeling, e.g., FLAG or other epitope tags, etc., will allow detection of receptor. This can be histological, as an affinity method for biochemical purification, or labeling or selection in an expression cloning approach. A two-hybrid selection system may also be applied making appropriate constructs with the available IL-1R sequences. See, e.g., Fields and Song (1989) Nature 340:245-246.

Generally, descriptions of IL-1Rs will be analogously applicable to individual specific embodiments directed to IL-1RD8, IL-1RD9, OR IL-1RD10 reagents and compositions.

The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the inventions to the specific embodiments.

20

EXAMPLES

I. General Methods

Some of the standard methods are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al. Biology Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York. Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Coligan, et al. (ed. 1996 and periodic supplements) Current Protocols In Protein Science Greene/Wiley, New York; Deutscher (1990) "Guide to Protein Purification" in Methods in Enzymology, vol. 182, and other volumes in

this series; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, N.J., or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to appropriate 5 segments, e.g., to a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1989) Chemische Industrie 12:69-70; Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic 10 Engineering, Principle and Methods 12:87-98, Plenum Press, N.Y.; and Crowe, et al. (1992) OIAexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc., Chatsworth, CA.

Computer sequence analysis is performed, e.g., using 15 available software programs, including those from the GCG (U. Wisconsin) and GenBank sources. Public sequence databases were also used, e.g., from GenBank, NCBI, SWISSPROT, and others.

Many techniques applicable to IL-10 receptors may be 20 applied to IL-1Rs, as described, e.g., in USSN 08/110,683 (IL-10 receptor), which is incorporated herein by reference for all purposes. Also, while many of the techniques described are directed to the IL-1RD9 reagents, corresponding methods will typically be 25 applicable with the IL-1RD8, and IL-1RD10 reagents. See also, USSN 60/065,776, filed November 17, 1997, and USSN 60/078,008, filed March 12, 1998, both of which are incorporated herein by reference.

30 II. Computational Analysis.

Human sequences related to IL-1Rs were identified from various EST databases using, e.g., the BLAST server (Altschul, et al. (1994) Nature Genet. 6:119-129). More sensitive pattern- and profile-based methods (Bork and 35 Gibson (1996) Meth. Enzymol. 266:162-184) were used to identify a fragment of a gene which exhibited certain homology to the IL-1Rs.

III. Cloning of full-length human IL-1R cDNAs.

PCR primers derived from the IL-1RD8, IL-1RD9, or IL-1RD10 sequences are used (Nomura, et al. (1994) DNA Res. 1:27-35) to probe an appropriate human cDNA library to yield a full length IL-1RD9 or IL-1RD10 cDNA sequence 5 or to probe a human erythroleukemic, TF-1 cell line-derived cDNA library (Kitamura, et al. (1989) Blood 73:375-380) to yield the IL-1R8 cDNA sequence. Full length cDNAs for human IL-1RD9 are cloned, e.g., by DNA hybridization screening of λ gt10 phage. PCR reactions 10 were conducted using *T. aquaticus* Taqplus DNA polymerase (Stratagene) under appropriate conditions.

IV. Localization of IL-1RD8, IL-1RD9, and IL-1RD10 mRNA

Human multiple tissue (Cat# 1, 2) and cancer cell 15 line blots (Cat# 7757-1), containing approximately 2 μ g of poly(A)⁺ RNA per lane, are purchased from Clontech (Palo Alto, CA). Probes are radiolabeled with [α -³²P] dATP, e.g., using the Amersham Rediprime random primer labeling kit (RPN1633). Prehybridization and 20 hybridizations are performed at 65° C in 0.5 M Na₂HPO₄, 7% SDS, 0.5 M EDTA (pH 8.0). High stringency washes are conducted, e.g., at 65° C with two initial washes in 2 x SSC, 0.1% SDS for 40 min followed by a subsequent wash in 0.1 x SSC, 0.1% SDS for 20 min. Membranes are then 25 exposed at -70° C to X-Ray film (Kodak) in the presence of intensifying screens. More detailed studies by cDNA library Southern blots are performed with selected human IL-1RD9 clones to examine their expression in hemopoietic or other cell subsets.

30 Two prediction algorithms that take advantage of the patterns of conservation and variation in multiply aligned sequences, PHD (Rost and Sander (1994) Proteins 19:55-72) and DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310), are used.

35 Alternatively, two appropriate primers are selected from Tables 1, 2, or 3. RT-PCR is used on an appropriate mRNA sample selected for the presence of message to produce a cDNA, e.g., a sample which expresses the gene.

Full length clones may be isolated by hybridization of cDNA libraries from appropriate tissues pre-selected by PCR signal. Northern blots can be performed.

Message for genes encoding, e.g., IL-1RD9 will be assayed by appropriate technology, e.g., PCR, immunoassay, hybridization, or otherwise. Tissue and organ cDNA preparations are available, e.g., from Clontech, Mountain View, CA. Identification of sources of natural expression are useful, as described. And the identification of functional receptor subunit pairings will allow for prediction of what cells express the combination of receptor subunits which will result in a physiological responsiveness to each of the IL-1 ligands.

The message for IL-1RD9 is quite rare, as it is not found with a degree of frequency in the available sequence databases. This suggests, e.g., a very rare message, or a highly restricted distribution. IL-1R9 is expressed predominantly on T cells, NK cells, monocytes and dendritic cells.

Southern Analysis on cDNA libraries can be performed: DNA (5 µg) from a primary amplified cDNA library is digested with appropriate restriction enzymes to release the inserts, run on a 1% agarose gel and transferred to a nylon membrane (Schleicher and Schuell, Keene, NH).

Samples for human mRNA isolation may include, e.g.: peripheral blood mononuclear cells (monocytes, T cells, NK cells, granulocytes, B cells), resting (T100); peripheral blood mononuclear cells, activated with anti-CD3 for 2, 6, 12 h pooled (T101); T cell, TH0 clone Mot 72, resting (T102); T cell, TH0 clone Mot 72, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T103); T cell, TH0 clone Mot 72, anergic treated with specific peptide for 2, 7, 12 h pooled (T104); T cell, TH1 clone HY06, resting (T107); T cell, TH1 clone HY06, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T108); T cell, TH1 clone HY06, anergic treated with specific peptide for 2, 6, 12 h pooled (T109); T cell, TH2 clone HY935, resting (T110); T cell, TH2 clone HY935, activated with anti-CD28 and anti-CD3 for 2, 7, 12 h pooled (T111);

T cells CD4+CD45RO- T cells polarized 27 days in anti-CD28, IL-4, and anti IFN- γ , TH2 polarized, activated with anti-CD3 and anti-CD28 4 h (T116); T cell tumor lines Jurkat and Hut78, resting (T117); T cell clones, pooled 5 AD130.2, Tc783.12, Tc783.13, Tc783.58, Tc782.69, resting (T118); T cell random $\gamma\delta$ T cell clones, resting (T119); Splenocytes, resting (B100); Splenocytes, activated with anti-CD40 and IL-4 (B101); B cell EBV lines pooled WT49, RSB, JY, CVIR, 721.221, RM3, HSY, resting (B102); B cell 10 line JY, activated with PMA and ionomycin for 1, 6 h pooled (B103); NK 20 clones pooled, resting (K100); NK 20 clones pooled, activated with PMA and ionomycin for 6 h (K101); NKL clone, derived from peripheral blood of LGL leukemia patient, IL-2 treated (K106); NK cytotoxic clone 15 640-A30-1, resting (K107); hematopoietic precursor line TF1, activated with PMA and ionomycin for 1, 6 h pooled (C100); U937 premonocytic line, resting (M100); U937 premonocytic line, activated with PMA and ionomycin for 1, 6 h pooled (M101); elutriated monocytes, activated 20 with LPS, IFN γ , anti-IL-10 for 1, 2, 6, 12, 24 h pooled (M102); elutriated monocytes, activated with LPS, IFN γ , IL-10 for 1, 2, 6, 12, 24 h pooled (M103); elutriated monocytes, activated with LPS, IFN γ , anti-IL-10 for 4, 16 h pooled (M106); elutriated monocytes, activated with 25 LPS, IFN γ , IL-10 for 4, 16 h pooled (M107); elutriated monocytes, activated LPS for 1 h (M108); elutriated monocytes, activated LPS for 6 h (M109); DC 70% CD1a+, from CD34+ GM-CSF, TNF α 12 days, resting (D101); DC 70% CD1a+, from CD34+ GM-CSF, TNF α 12 days, activated with 30 PMA and ionomycin for 1 hr (D102); DC 70% CD1a+, from CD34+ GM-CSF, TNF α 12 days, activated with PMA and ionomycin for 6 hr (D103); DC 95% CD1a+, from CD34+ GM-CSF, TNF α 12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D104); DC 95% CD14+, ex 35 CD34+ GM-CSF, TNF α 12 days FACS sorted, activated with PMA and ionomycin 1, 6 hr pooled (D105); DC CD1a+ CD86+, from CD34+ GM-CSF, TNF α 12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D106); DC from monocytes GM-CSF, IL-4 5 days, resting (D107); DC from

monocytes GM-CSF, IL-4 5 days, resting (D108); DC from monocytes GM-CSF, IL-4 5 days, activated LPS 4, 16 h pooled (D109); DC from monocytes GM-CSF, IL-4 5 days, activated TNF α , monocyte supe for 4, 16 h pooled (D110);

5 leiomyoma L11 benign tumor (X101); normal myometrium M5 (O115); malignant leiomyosarcoma GS1 (X103); lung fibroblast sarcoma line MRC5, activated with PMA and ionomycin for 1, 6 h pooled (C101); kidney epithelial carcinoma cell line CHA, activated with PMA and ionomycin

10 for 1, 6 h pooled (C102); kidney fetal 28 wk male (O100); lung fetal 28 wk male (O101); liver fetal 28 wk male (O102); heart fetal 28 wk male (O103); brain fetal 28 wk male (O104); gallbladder fetal 28 wk male (O106); small intestine fetal 28 wk male (O107); adipose tissue fetal

15 28 wk male (O108); ovary fetal 25 wk female (O109); uterus fetal 25 wk female (O110); testes fetal 28 wk male (O111); spleen fetal 28 wk male (O112); adult placenta 28 wk (O113); and tonsil inflamed, from 12 year old (X100); psoriasis human skin sample; normal human skin sample;

20 pool of rheumatoiod arthritis human; Hashimoto's thryroiditis thryroid; normal human throid; ulceratived colitis human colon; normal human colon; normal weight monkey colon; pheumocysitc carnii pneumonia lung; allergic lung; pool of three heavy smoker human lung;

25 pool of two normal human lung; Ascaris-challenged monkey lung, 24hr; Ascaris-challenged monkey lung, 4hr; normal weight monkey lung..

IL-1RD8 message is described below in Table 5.

30 There appears to be a correlation between developmental stage of tissues and the levels of messages: fetal and transformed tissues express high levels, whereas normal, adult tissues express low levels (with the exception of skeletal muscle). Further insights into this phenomenon will need further experiments.

35 Message for genes encoding IL-1RD8 will be assayed by appropriate technology, e.g., PCR, immunoassay, hybridization, or otherwise. Tissue and organ cDNA preparations are available, e.g., from Clontech, Mountain View, CA. Identification of sources of natural

expression are useful, as described. And the identification of functional receptor subunit pairings will allow for prediction of what cells express the combination of receptor subunits which will result in a physiological responsiveness to each of the IL-1 ligands.

Table 5

Multiple Tissue Northern Blots were screened with a radiolabeled probe, encompassing the cytoplasmic region of Interleukin-1 receptor R8 (IL-1RD8). The results are summarized below: In all cases listed there is a smaller band at 3.4 Kb and in a few cases a larger band at 4.0 Kb as well.			
	Tissue	3.4 kb	4.0 kb
15	Spleen	weak	
	Thymus	weak	
	Prostate	weak	
20	Testis	weak	
	Ovary	weak	
	Small Intestine	weak	
	Colon (mucosal lining)	weak	
25	Peripheral Blood Leukocyte	weak	
	Heart	moderate	
	Brain	weak	
	Placenta	moderate	
	Lung	weak	
	Liver	weak	
30	Skeletal Muscle	strong	
	Kidney	weak	
	Pancreas	weak	
	Fetal brain	strong	weak
	Fetal lung	strong	weak
35	Fetal Liver	strong	weak
	Fetal Kidney	strong	weak
	proleukocytic leukemia HL-60	strong	
	HeLa Cell S3	very strong	weak
40	Chronic myelogenous leukemia, K-562	very strong	weak
	Lymphoblastic leukemia, MOLT-4	weak	
	Burkitt's lymphoma Rajii	moderate	
	Colorectal adenocarcinoma SW40	very strong	strong
	Lung carcinoma A549	strong	strong
45	Melanoma	very strong	weak

V. Cloning of species counterparts of IL-1RDs

50 Various strategies are used to obtain species counterparts of IL-1RD8, IL-1RD9, and IL-1RD10 preferably from other primates. One method is by cross hybridization using closely related species DNA probes. It may be useful to go into evolutionarily similar species as intermediate steps. Another method is by using specific PCR primers based on the identification of

blocks of similarity or difference between genes, e.g., areas of highly conserved or nonconserved polypeptide or nucleotide sequence. In addition, gene sequence databases may be screened for related sequences from 5 other species.

VI. Production of mammalian IL-1RD8, IL-1RD9, and IL-1RD10 protein

An appropriate, e.g., GST, fusion construct is 10 engineered for expression, e.g., in *E. coli*. For example, a mouse IGIF pGex plasmid is constructed and transformed into *E. coli*. Freshly transformed cells are grown, e.g., in LB medium containing 50 µg/ml ampicillin and induced with IPTG (Sigma, St. Louis, MO). After 15 overnight induction, the bacteria are harvested and the pellets containing, e.g., the IL-1R8 polypeptide are isolated. The pellets are homogenized, e.g., in TE buffer (50 mM Tris-base pH 8.0, 10 mM EDTA and 2 mM pefabloc) in 2 liters. This material is passed through a 20 microfluidizer (Microfluidics, Newton, MA) three times. The fluidized supernatant is spun down on a Sorvall GS-3 rotor for 1 h at 13,000 rpm. The resulting supernatant containing the IL-1R polypeptide is filtered and passed over a glutathione-SEPHAROSE column equilibrated in 50 mM 25 Tris-base pH 8.0. The fractions containing the IL-1RD9-GST fusion protein are pooled and cleaved, e.g., with thrombin (Enzyme Research Laboratories, Inc., South Bend, IN). The cleaved pool is then passed over a Q-SEPHAROSE column equilibrated in 50 mM Tris-base. Fractions 30 containing IL-1RD9 are pooled and diluted in cold distilled H₂O, to lower the conductivity, and passed back over a fresh Q-Sepharose column, alone or in succession with an immunoaffinity antibody column. Fractions containing the IL-1RD9 polypeptide are pooled, aliquoted, 35 and stored in the -70° C freezer.

Comparison of the CD spectrum with IL-1R polypeptide may suggest that the protein is correctly folded. See Hazuda, et al. (1969) J. Biol. Chem. 264:1689-1693.

VII. Determining physiological forms of receptors

The IL-1 α and IL-1 β ligands bind an IL-1RD1 as the primary receptor and this complex then forms a high affinity receptor complex with the IL-1RD3. Such

5 receptor subunits are probably shared with the receptors for the new IL-1 ligand family members. See, e.g., USSN 60/044,165 and USSN 60/055,111. Combination of the IL-1RD9 (α subunit type, based upon sequence analysis) will combine with the IL-1RD5 (β subunit type, based upon
10 sequence analysis) to form a heterodimer receptor. The IL-1 δ and IL-1 ϵ ligands each probably signal through a receptor comprising the association of IL-1RD4, IL-1RD6, or IL-1RD9 (alpha components) with IL-1RD3, IL-1RD8, or IL-1RD10 (beta components).

15 These defined subunit combinations can be tested now with the provided reagents. In particular, appropriate constructs can be made for transformation or transfection of subunits into cells. Constructs for the alpha chains, e.g., IL-1RD1, IL-1RD4, IL-1RD6, and IL-1RD9 forms can be
20 made. Likewise for the beta subunits IL-1RD3, IL-1RD5, IL-1RD7, and IL-1RD8. Structurally, the IL-1RD10 is most similar to the IL-1RD8, suggesting that it may also be a beta receptor subunit. Combinatorial transfections of transformations can make cells expressing defined
25 subunits, which can be tested for response to each of the IL-1 ligands. Appropriate cell types can be used, e.g., 293 T cells, Jurkat cells, with, e.g., a nuclear kappa B (NF κ B)-controlled luciferase reporter construct such as described e.g., in Otieno et al., (1997) Am J Physiol
30 273-xxx.

Such combinations of various IL-1 ligands and receptors were tested to determine if a functional signaling complex had been formed using an NF κ B-controlled luciferase reporter construct to indicate
35 formation of a functional signaling complex (+) or failure to form a functional signaling complex (-). The results, presented below,

IL-1 α + IL-1 β + IL-1RD1 + IL-1RD3 = +;

IL-1 α + IL-1 β + IL-1RD1 + IL-1RD5 = +;
IL-1 α + IL-1 β + IL-1RD1 + IL-1RD8 = +;
IL-1 α + IL-1 β + IL-1RD1 + IL-1RD10 may = +/?;

5 suggest that IL-1RD3, IL-1RD5, IL-1RD8, and IL-1RD10 may functionally substitute for each other when in combination with IL-1 α + IL-1 β + IL-1RD1.

10 Other combinations (below) demonstrate a failure of functional substitution; suggesting the importance of contextual dependence on substitution e.g., IL-1RD3, and IL-1RD8 cannot functionally replace IL-1RD5 in the following combination: IL-1 γ + IL-1RD9 + IL-1RD5.

15 IL-1 γ + IL-1RD9 + IL-1RD5 = +;
IL-1 γ + IL-1RD9 + IL-1RD3 = -;
IL-1 γ + IL-1RD9 + IL-1RD8 = -;

20 A further series of experiments tested the ability of mouse (m) and human (h) homologues to functionally substitute for each other. The results, shown below,

25 mIL-1 γ + mIL-1RD5 + mIL-1RD9 = +;
mIL-1 γ + mIL-1RD5 + hIL-1RD9 = -;
mIL-1 γ + hIL-1RD5 + hIL-1RD9 = -;
mIL-1 γ + hIL-1RD5 + mIL-1RD9 = -;
30 hIL-1 γ + mIL-1RD5 + mIL-1RD9 = -;
hIL-1 γ + mIL-1RD5 + hIL-1RD9 = -;
hIL-1 γ + hIL-1RD5 + mIL-1RD9 = -;
hIL-1 γ + hIL-1RD5 + hIL-1RD9 = +;

suggest that species homogeneity is required to form a functioning complex in this particular constellation of ligand and receptor units.

35 Biological assays will generally be directed to the ligand binding feature of the protein or to the kinase/phosphatase activity of the receptor. The activity will typically be reversible, as are many other enzyme actions mediate phosphatase or phosphorylase

activities, which activities are easily measured by ... standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738.

The family of interleukins 1 contains molecules, each of which is an important mediator of inflammatory disease. For a comprehensive review, see Dinarello (1996) "Biologic basis for interleukin-1 in disease" Blood 87:2095-2147. There are suggestions that the various IL-1 ligands may play important roles in the initiation of disease, particularly inflammatory responses. The finding of novel polypeptides related to the IL-1 family furthers the identification of molecules that provide the molecular basis for initiation of disease and allow for the development of therapeutic strategies of increased range and efficacy.

VIII. Preparation of antibodies specific for IL-1Rs

Inbred Balb/c mice are immunized intraperitoneally with recombinant forms of the polypeptide, e.g., purified IL-1RD8, IL-1RD9, and IL-1RD10, or stable transfected NIH-3T3 cells. Animals are boosted at appropriate time points with protein, with or without additional adjuvant, to further stimulate antibody production. Serum is collected, or hybridomas produced with harvested spleens.

Alternatively, Balb/c mice are immunized with cells transformed with the gene or fragments thereof, either endogenous or exogenous cells, or with isolated membranes enriched for expression of the antigen. Serum is collected at the appropriate time, typically after numerous further administrations. Various gene therapy techniques may be useful, e.g., in producing protein *in situ*, for generating an immune response.

Monoclonal antibodies may be made. For example, splenocytes are fused with an appropriate fusion partner

and hybridomas are selected in growth medium by standard procedures. Hybridoma supernatants are screened for the presence of antibodies which bind to the desired IL-1R, e.g., by ELISA or other assay. Antibodies which 5 selectively recognize specific IL-1R embodiments may also be selected or prepared.

In another method, synthetic peptides or purified protein are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan 10 (1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. In appropriate situations, the binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a 15 substrate for panning methods. Nucleic acids may also be introduced into cells in an animal to produce the antigen, which serves to elicit an immune response. See, e.g., Wang, et al. (1993) Proc. Nat'l. Acad. Sci. 90:4156-4160; Barry, et al. (1994) BioTechniques 16:616-20 619; and Xiang, et al. (1995) Immunity 2:129-135.

Moreover, antibodies which may be useful to determine the combination of the IL-1RD8, IL-1RD9, or IL-1RD10 with a functional beta subunit may be generated. Thus, e.g., epitopes characteristic of a particular 25 functional alpha/beta combination may be identified with appropriate antibodies.

IX. Production of fusion proteins with IL-1Rs

Various fusion constructs are made with IL-1Rs. A 30 portion of the appropriate gene is fused to an epitope tag, e.g., a FLAG tag, or to a two hybrid system construct. See, e.g., Fields and Song (1989) Nature 340:245-246.

The epitope tag may be used in an expression cloning 35 procedure with detection with anti-FLAG antibodies to detect a binding partner, e.g., ligand for the respective IL-1R. The two hybrid system may also be used to isolate proteins which specifically bind, e.g., to IL-1RD9.

X. Structure activity relationship

Information on the criticality of particular residues is determined using standard procedures and analysis. Standard mutagenesis analysis is performed, 5 e.g., by generating many different variants at determined positions, e.g., at the positions identified above, and evaluating biological activities of the variants. This may be performed to the extent of determining positions which modify activity, or to focus on specific positions 10 to determine the residues which can be substituted to either retain, block, or modulate biological activity.

Alternatively, analysis of natural variants can indicate what positions tolerate natural mutations. This may result from population analysis of variation among 15 individuals, or across strains or species. Samples from selected individuals are analyzed, e.g., by PCR analysis and sequencing. This allows evaluation of population polymorphisms.

20 XI. Isolation of a ligand for IL-1Rs

An IL-1R can be used as a specific binding reagent to identify its binding partner, by taking advantage of its specificity of binding, much like an antibody would be used. Typically, the binding receptor is a 25 heterodimer of receptor subunits. A binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods.

The binding composition is used to screen an 30 expression library made from a cell line which expresses a binding partner, i.e., ligand, preferably membrane associated. Standard staining techniques are used to detect or sort surface expressed ligand, or surface expressing transformed cells are screened by panning. 35 Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

For example, on day 0, precoat 2-chamber permanox slides with 1 ml per chamber of fibronectin, 10 ng/ml in

PBS, for 30 min at room temperature. Rinse once with PBS. Then plate COS cells at 2-3 x 10⁵ cells per chamber in 1.5 ml of growth media. Incubate overnight at 37° C.

On day 1 for each sample, prepare 0.5 ml of a 5 solution of 66 µg/ml DEAE-dextran, 66 µM chloroquine, and 4 µg DNA in serum free DME. For each set, a positive control is prepared, e.g., of IL-1R-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with serum free DME. Add the DNA solution and incubate 5 hr 10 at 37° C. Remove the medium and add 0.5 ml 10% DMSO in DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium and incubate overnight.

On day 2, change the medium. On days 3 or 4, the cells are fixed and stained. Rinse the cells twice with 15 Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS. The slides may be stored at -80° C after all liquid is removed. For each chamber, 0.5 ml incubations are performed as follows. Add HBSS/saponin (0.1%) with 20 32 µl/ml of 1 M NaN₃ for 20 min. Cells are then washed with HBSS/saponin 1X. Add appropriate IL-1R or IL-1R/antibody complex to cells and incubate for 30 min. Wash cells twice with HBSS/saponin. If appropriate, add first antibody for 30 min. Add second antibody, e.g., 25 Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector Elite ABC horseradish peroxidase solution, and preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1 drop solution B (biotin) per 2.5 ml 30 HBSS/saponin. Wash cells twice with HBSS/saponin. Add ABC HRP solution and incubate for 30 min. Wash cells twice with HBSS, second wash for 2 min, which closes cells. Then add Vector diaminobenzoic acid (DAB) for 5 to 10 min. Use 2 drops of buffer plus 4 drops DAB plus 2 drops of H₂O₂ per 5 ml of glass distilled water. 35 Carefully remove chamber and rinse slide in water. Air dry for a few minutes, then add 1 drop of Crystal Mount and a cover slip. Bake for 5 min at 85-90° C.

Evaluate positive staining of pools and progressively subclone to isolation of single genes responsible for the binding.

Alternatively, IL-1R reagents are used to affinity 5 purify or sort out cells expressing a putative ligand. See, e.g., Sambrook, et al. or Ausubel, et al.

Another strategy is to screen for a membrane bound receptor by panning. The receptor cDNA is constructed as described above. The ligand can be immobilized and used 10 to immobilize expressing cells. Immobilization may be achieved by use of appropriate antibodies which recognize, e.g., a FLAG sequence of an IL-1R fusion construct, or by use of antibodies raised against the first antibodies. Recursive cycles of selection and 15 amplification lead to enrichment of appropriate clones and eventual isolation of receptor expressing clones.

Phage expression libraries can be screened by mammalian IL-1Rs. Appropriate label techniques, e.g., anti-FLAG antibodies, will allow specific labeling of 20 appropriate clones.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The 25 specific embodiments described herein are offered by way of example only, and the invention is to be limited by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled; and the invention is not to be limited by the specific 30 embodiments that have been presented herein by way of example.

WHAT IS CLAIMED IS:

1. An isolated or recombinant IL-1RD9 polypeptide:

- a) consisting of SEQ ID NO: 6, 8, 10, 12, 14, or 16;
- b) encoded by a polynucleotide comprising the open reading frame of SEQ ID NO: 5, 7, 9, 11, 13, or 15; or
- c) encoded by a naturally occurring allelic variant of a polynucleotide comprising the open reading frame of SEQ ID NO: 5, 7, 9, 11, 13, or 15.

10 2. The polypeptide of claim 1, encoded by a naturally

15 occurring allelic variant of a polynucleotide comprising

the open reading frame of SEQ ID NO: 5, 7, 9, 11, 13, or 15.

3. An isolated or recombinant IL-1RD9 polypeptide

which:

20 a) has an apparent molecular weight 68.3 kD as determined by SDS/polyacrylamide gel electrophoresis;

b) has an estimated pI of 9.04; and

c) is found on T cells; and

25 wherein said polypeptide has at least one of the

following properties:

i) is a heterodimer;

iii) is an IL-1 α subunit type, or

iii) when brought into contact with IL-1RD5 and IL-

30 1 α , for a sufficient time, forms a functional

high affinity receptor complex that activates

an NF κ B transcription factor reporter

construct.

35 4. An isolated or recombinant polypeptide comprising a segment of contiguous amino acid residues selected from the following group:

- a) 15 contiguous amino acid residues of said polypeptide of claim 2;

- b) 20 contiguous amino acid residues of said polypeptide of claim 2;
- c) 25 contiguous amino acid residues of said polypeptide of claim 2;
- 5 d) 30 contiguous amino acid residues of said polypeptide of claim 2;
- e) 35 contiguous amino acid residues of said polypeptide of claim 2; or
- f) 40 contiguous amino acid residues of said polypeptide

10 of claim 2.

5. The polypeptide of claim 1 which is immunogenic.

6. An isolated or recombinant polypeptide comprising an
15 immunogenic peptide of said polypeptide of claim 3.

7. An isolated or recombinant polypeptide comprising an immunogenic polypeptide of claim 4.

20 8. A fusion protein comprising said polypeptide of claim 4 and:

- a) a detection or purification tag selected from the group consisting of a FLAG, His6, and immunoglobulin peptide;
- 25 b) a carrier protein selected from the group consisting of keyhole limpet hemocyanin, bovine serum albumin, and tetanus toxoid; or
- c) another peptide selected from the group consisting of luciferase, bacterial β -galactosidase, trpE, protein A, β -lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor.

30 9. A fusion protein comprising said polypeptide of claim 5 and:

- a) a detection or purification tag selected from the group consisting of a FLAG, His6, and immunoglobulin peptide;

- b) a carrier protein selected from the group ...
consisting of keyhole limpet hemocyanin, bovine serum albumin, the tetanus toxoid; or
- c) another peptide selected from the group
consisting of luciferase, bacterial β -galactosidase, trpE, protein A, β -lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor.

10 10. A composition comprising said polypeptide of claim 1, that is:

- a) in a pharmaceutically acceptable carrier;
- b) in a sterile composition;
- c) in a buffered solution; or
- 15 d) in an aqueous suspension.

11. A composition comprising said polypeptide of claim 4, that is:

- a) in a pharmaceutically acceptable carrier;
- 20 b) in a sterile composition;
- c) in a buffered solution; or
- d) in an aqueous suspension.

12. A polypeptide of claim 4, that is:

- 25 a) denatured;
- b) immunopurified;
- c) attached to a solid substrate;
- d) detectably labeled; or
- e) chemically synthesized.

30 13. A polypeptide of claim 5, that is:

- a) denatured;
- b) immunopurified;
- c) attached to a solid substrate;
- 35 d) detectably labeled; or
- e) chemically synthesized.

14. A kit comprising said polypeptide of claim 1, and:

- a) a compartment comprising said protein; or

- b) instructions for use or disposal of reagents in said kit.

15. A kit comprising said polypeptide of claim 4, and:

- 5 a) a compartment comprising said protein; or
- b) instructions for use or disposal of reagents in said kit.

16. A method of raising an antibody, comprising immunizing an animal with a polypeptide of claim 5.

17. A method of producing an antibody:antigen complex, comprising contacting a polypeptide of claim 5 with an antibody which specifically binds said polypeptide, thereby forming said complex.

18. A composition of matter selected from the group consisting of:

- a) a substantially pure or recombinant IL-1RD8 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 4;
- b) a natural sequence IL-1RD8 comprising SEQ ID NO: 4;
- 25 c) a fusion polypeptide comprising IL-1RD8 sequence;
- d) a substantially pure or recombinant IL-1RD10 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 20;
- e) a natural sequence IL-1RD10 comprising SEQ ID NO: 20; and
- f) a fusion protein comprising IL-1RD10 sequence.

35 19. A substantially pure or isolated polypeptide comprising a segment exhibiting sequence identity to a corresponding portion of an:

- a) IL-1RD8 of claim 18, wherein:

- x) is attached to a solid substrate;
- xi) is conjugated to another chemical moiety;
- xii) is a 5-fold or less substitution from natural sequence; or
- 5 xiii) is a deletion or insertion variant from a natural sequence.

21. A composition comprising:

- 10 a) a sterile IL-1RD8 polypeptide of claim 18;
- b) said IL-1RD8 protein or peptide of claim 18 and a carrier, wherein said carrier is:
 - i) an aqueous compound, including water, saline, and/or buffer; and/or
 - 15 ii) formulated for oral, rectal, nasal, topical, or parenteral administration;
- c) a sterile IL-1RD10 polypeptide of claim 18; or
- d) said IL-1RD10 polypeptide of claim 18 and a carrier, wherein said carrier is:
 - i) an aqueous compound, including water, saline, and/or buffer; and/or
 - 20 ii) formulated for oral, rectal, nasal, topical, or parenteral administration.

21. A fusion protein of claim 18, comprising:

- 25 a) mature protein sequence of SEQ ID NO: 2, 4, 18 or 20;
- b) a detection or purification tag, including a FLAG, His6, or Ig sequence; or
- c) sequence of another receptor protein.

30

22. A kit comprising a polypeptide of claim 18, and:

- a) a compartment comprising said polypeptide; and/or
- 35 b) instructions for use or disposal of reagents in said kit.

23. A binding compound comprising an antigen binding site from an antibody, which specifically binds to a natural:

A) IL-1RD8 protein of claim 18, wherein:

- a) said protein is a primate or rodent protein;
- b) said binding compound is an Fv, Fab, or Fab2 fragment;
- c) said binding compound is conjugated to another chemical moiety; or
- d) said antibody:
 - i) is raised against a peptide sequence of a mature polypeptide of Seq ID NO 2 or 4;
 - ii) is raised against a mature primate or rodent IL-1RD8;
 - iii) is raised to a purified human IL-1RD8;
 - iv) is raised to a purified mouse IL-1RD8;
 - v) is immunoselected;
 - vi) is a polyclonal antibody;
 - vii) binds to a denatured IL-1RD8;
 - viii) exhibits a Kd to antigen of at least 30 μ M;
 - ix) is attached to a solid substrate, including a bead or plastic membrane;
 - x) is in a sterile composition; or
 - xi) is detectably labeled, including a radioactive or fluorescent label; or

B) IL-1RD10 polypeptide of claim 18, wherein:

- a) said polypeptide is a primate polypeptide;
- b) said binding compound is an Fv, Fab, or Fab2 fragment;
- c) said binding compound is conjugated to another chemical moiety; or
- d) said antibody:
 - i) is raised against a peptide sequence of a mature polypeptide of SEQ ID NO: 18 or 20;
 - ii) is raised against a mature primate IL-1RD10;

- iii) is raised to a purified human IL-1RD10;
- iv) is immunoselected;
- v) is a polyclonal antibody;
- 5 vi) binds to a denatured IL-1RD10;
- vii) exhibits a Kd to antigen of at least 30 μ M;
- viii) is attached to a solid substrate, including a bead or plastic membrane;
- 10 ix) is in a sterile composition; or
- x) is detectably labeled, including a radioactive or fluorescent label

24. A kit comprising said binding compound of claim 25, 15 and:

- a) a compartment comprising said binding compound; and/or
- b) instructions for use or disposal of reagents in said kit.

20

26. A method of:

- A) making an antibody of claim 23, comprising immunizing an immune system with an immunogenic amount of:
 - a) a primate IL-1RD8 polypeptide;
 - b) a primate IL-1RD10 polypeptide; or thereby causing said antibody to be produced; or
- 25 B) producing an antigen:antibody complex, comprising contacting:
 - a) a primate IL-1RD8 polypeptide with an antibody of claim 23A; or
 - b) a primate IL-1RD10 polypeptide with an antibody of claim 23B;
- 30 35 thereby allowing said complex to form.

27. A composition comprising:

- a) a sterile binding compound of claim 23, or

b) said binding compound of claim 23 and a carrier, wherein said carrier is:

- i) an aqueous compound, including water, saline, and/or buffer; and/or
- 5 ii) formulated for oral, rectal, nasal, topical, or parenteral administration.

28. An isolated or recombinant nucleic acid encoding a protein or peptide or fusion protein of claim 18, 10 wherein:

- a) said IL-1RD8 or IL-1RD10 is from a mammal; or
- b) said nucleic acid:
 - i) encodes an antigenic polypeptide sequence of SEQ ID NO: 2, 4, 18 or 20;
 - 15 ii) encodes a plurality of antigenic polypeptide sequences of SEQ ID NO: 2, 4, 18 or 20;
 - iii) exhibits identity to a natural cDNA encoding said segment;
 - 20 iv) is an expression vector;
 - v) further comprises an origin of replication;
 - vi) is from a natural source;
 - vii) comprises a detectable label;
 - viii) comprises synthetic nucleotide sequence;
 - 25 ix) is less than 6 kb, preferably less than 3 kb;
 - x) is from a mammal, including a primate, such as a human;
 - xi) comprises a natural full length coding sequence;
 - 30 xii) is a hybridization probe for a gene encoding said IL-1RD8 or IL-1RD10;
 - xiii) comprises a plurality of nonoverlapping segments of at least 15 nucleotides from SEQ ID NO: 1, 3, 17 or 19; or
 - 35 xiv) is a PCR primer, PCR product, or mutagenesis primer.

29. A cell transfected or transformed with a recombinant nucleic acid of claim 28.

30. The cell of claim 29, wherein said cell is:

- 5 a) a prokaryotic cell;
- b) a eukaryotic cell;
- c) a bacterial cell;
- d) a yeast cell;
- e) an insect cell;
- 10 f) a mammalian cell;
- g) a mouse cell;
- h) a primate cell; or
- i) a human cell.

15 31. A kit comprising said nucleic acid of claim 28, and:

- a) a compartment comprising said nucleic acid;
- b) a compartment further comprising a primate or rodent IL-1RD8 or primate IL-1RD10 polypeptide; and/or
- 20 b) instructions for use or disposal of reagents in said kit.

32. A method of:

- 25 A) making a polypeptide, comprising expressing said nucleic acid of claim 28, thereby producing said polypeptide; or
- B) making a duplex nucleic acid, comprising contacting said nucleic acid of claim 28 with a hybridizing nucleic acid, thereby allowing said duplex to form.

33. A nucleic acid which:

- 35 a) hybridizes under wash conditions of 40° C and less than 2M salt to SEQ ID NO: 3 or 19; or
- b) exhibits identity over a stretch of at least about 30 nucleotides to a primate IL-1RD8 or IL-1RD10.

34. The nucleic acid of claim 33, wherein:

- a) said wash conditions are at 55° C and/or 500 mM salt; or
- b) said stretch is at least 55 nucleotides.

5 35. The nucleic acid of claim 34, wherein:

- a) said wash conditions are at 65° C and/or 150 mM salt; or
- b) said stretch is at least 75 nucleotides.

10 36. A method of modulating physiology or development of a cell or tissue culture cells comprising contacting said cell with an agonist or antagonist of a primate IL-1RD8 or IL-1RD10.

15 37. The method of claim 36, wherein said cell is transformed with a nucleic acid encoding either an IL-1RD8 or IL-1RD10, and another IL-1R.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Schering Corporation

(ii) TITLE OF INVENTION: HUMAN RECEPTOR PROTEINS; RELATED REAGENTS

(iii) NUMBER OF SEQUENCES: 33

(iv) CORRESPONDENCE ADDRESS:

- (A) ADDRESSEE: Schering-Plough Corporation
- (B) STREET: 2000 Galloping Hill Road
- (C) CITY: Kenilworth
- (D) STATE: New Jersey
- (E) COUNTRY: USA
- (F) ZIP: 07033-0530

(v) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE: Floppy disk
- (B) COMPUTER: IBM PC compatible
- (C) OPERATING SYSTEM: PC-DOS/MS-DOS
- (D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:

- (A) APPLICATION NUMBER:
- (B) FILING DATE:
- (C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: US 60/078,008
- (B) FILING DATE: 12-MAR-1998

(vii) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: US 60/081,883
- (B) FILING DATE: 15-APR-1998

(vii) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: US 60/095,987
- (B) FILING DATE: 10-AUG-1998

(vii) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: US 08/971,635
- (B) FILING DATE: 17-NOV-1997

(vii) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: US 09/040,714
- (B) FILING DATE: 18-MAR-1998

(vii) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: US 08/951,829
- (B) FILING DATE: 15-OCT-1997

(ix) TELECOMMUNICATION INFORMATION:

- (A) TELEPHONE: (908) 298-2135
- (B) TELEFAX: (908) 298-5388

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1737 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1737

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 342..343
- (D) OTHER INFORMATION: /note= "splice junction"

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 453..454
- (D) OTHER INFORMATION: /note= "splice junction"

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 756..757
- (D) OTHER INFORMATION: /note= "splice junction"

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 885..886
- (D) OTHER INFORMATION: /note= "splice junction"

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 1033..1034
- (D) OTHER INFORMATION: /note= "splice junction"

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 1177..1178
- (D) OTHER INFORMATION: /note= "splice junction"

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 1350..1351
- (D) OTHER INFORMATION: /note= "splice junction"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TTA CTG CTC ACA CTA TTA GTG TCA ACA ATG CTC ACT GTA TCT TAT ACC
 Leu Leu Leu Thr Leu Leu Val Ser Thr Met Leu Thr Val Ser Tyr Thr
 1 5 10 15

48

TCT TCT GAT TTT CTT TCA GTG GAT GGC TGC ATT GAC TGG TCA GTG GAT
 Ser Ser Asp Phe Leu Ser Val Asp Gly Cys Ile Asp Trp Ser Val Asp
 20 25 30

96

CTC AAG ACA TAC ATG GCT TTG GCA GGT GAA CCA GTC CGA GTG AAA TGT Leu Lys Thr Tyr Met Ala Leu Ala Gly Glu Pro Val Arg Val Lys Cys 35 40 45	144
GCC CTT TTC TAC AGT TAT ATT CGT ACC AAC TAT AGC ACG GCC CAG AGC Ala Leu Phe Tyr Ser Tyr Ile Arg Thr Asn Tyr Ser Thr Ala Gln Ser 50 55 60	192
ACT GGG CTC AGG CTT ATG TGG TAC AAA AAC AAA GGT GAT TTG GAA GAG Thr Gly Leu Arg Leu Met Trp Tyr Lys Asn Lys Gly Asp Leu Glu Glu 65 70 75 80	240
CCC ATC ATC TTT TCA GAG GTC AGG ATG AGC AAA GAG GAA GAT TCA ATA Pro Ile Ile Phe Ser Glu Val Arg Met Ser Lys Glu Glu Asp Ser Ile 85 90 95	288
TGG TTT CAC TCA GCT GAG GCA CAA GAC AGT GGA TTC TAC ACT TGT GTT Trp Phe His Ser Ala Glu Ala Gln Asp Ser Gly Phe Tyr Thr Cys Val 100 105 110	336
TTA AGG AAC TCA ACA TAT TGC ATG AAG GTG TCA ATG TCC TTG ACT GTT Leu Arg Asn Ser Thr Tyr Cys Met Lys Val Ser Met Ser Leu Thr Val 115 120 125	384
GCA GAG AAT GAA TCA GGC CTG TGC TAC AAC AGC AGG ATC CGC TAT TTA Ala Glu Asn Glu Ser Gly Leu Cys Tyr Asn Ser Arg Ile Arg Tyr Leu 130 135 140	432
GAA AAA TCT GAA GTC ACT AAA AGA AAG GAG ATC TCC TGT CCA GAC ATG Glu Lys Ser Glu Val Thr Lys Arg Lys Glu Ile Ser Cys Pro Asp Met 145 150 155 160	480
GAT GAC TTT AAA AAG TCC GAT CAG GAG CCT GAT GTT GTG TGG TAT AAG Asp Asp Phe Lys Lys Ser Asp Gln Glu Pro Asp Val Val Trp Tyr Lys 165 170 175	528
GAA TGC AAG CCA AAA ATG TGG AGA AGC ATA ATA ATA CAG AAA GGA AAT Glu Cys Lys Pro Lys Met Trp Arg Ser Ile Ile Ile Gln Lys Gly Asn 180 185 190	576
GCT CTT CTG ATC CAA GAA GTT CAA GAA GAA GAT GGA GGA AAT TAC ACA Ala Leu Leu Ile Gln Glu Val Gln Glu Glu Asp Gly Gly Asn Tyr Thr 195 200 205	624
TGT GAA CTT AAA TAT GAA GGA AAA CTT GTA AGA CGA ACA ACT GAA TTG Cys Glu Leu Lys Tyr Glu Gly Lys Leu Val Arg Arg Thr Thr Glu Leu 210 215 220	672
AAA GTT ACA GCT TTA CTC ACA GAC AAG CCT CCC AAG CCA TTG TTC CCC Lys Val Thr Ala Leu Leu Thr Asp Lys Pro Pro Lys Pro Leu Phe Pro 225 230 235 240	720
ATG GAG AAT CAG CCA AGT GTT ATA GAT GTC CAG CTG GGT AAG CCT CTG Met Glu Asn Gln Pro Ser Val Ile Asp Val Gln Leu Gly Lys Pro Leu 245 250 255	768
AAC ATC CCC TGC AAA GCA TTC TTC GGA TTC AGT GGA GAG TCT GGG CCA Asn Ile Pro Cys Lys Ala Phe Phe Gly Ser Gly Glu Ser Gly Pro 260 265 270	816
ATG ATC TAC TGG ATG AAA GGA GAA AAG TTT ATT GAA GAA CTG GCA GGT Met Ile Tyr Trp Met Lys Gly Glu Lys Phe Ile Glu Glu Leu Ala Gly 275 280 285	864

CAC ATT AGA GAA GGT GAA ATA AGG CTT CTC AAA GAG CAT CTT GGA GAA His Ile Arg Glu Gly Glu Ile Arg Leu Leu Lys Glu His Leu Gly Glu 290 295 300	912
AAA GAA GTT GAA TTG GCA CTC ATC TTT GAC TCA GTT GTG GAA GCT GAC Lys Glu Val Glu Leu Ala Leu Ile Phe Asp Ser Val Val Glu Ala Asp 305 310 315 320	960
CTG GCG AAT TAT ACC TGC CAT GTT GAA AAC CGA AAT GGA CGG AAA CAT Leu Ala Asn Tyr Thr Cys His Val Glu Asn Arg Asn Gly Arg Lys His 325 330 335	1008
GCC AGT GTT TTG CTG CGT AAA AAG GAT TTA ATC TAT AAA ATT GAG CTT Ala Ser Val Leu Leu Arg Lys Lys Asp Leu Ile Tyr Lys Ile Glu Leu 340 345 350	1056
GCA GGG GGC CTG GGA GCA ATC TTC CTC CTC CTT GTA CTG CTG GTG GTC Ala Gly Gly Leu Gly Ala Ile Phe Leu Leu Val Leu Leu Val Val 355 360 365	1104
ATT TAC AAA TGC TAC AAC ATT GAA TTG ATG CTC TTC TAC AGG CAG CAC Ile Tyr Lys Cys Tyr Asn Ile Glu Leu Met Leu Phe Tyr Arg Gln His 370 375 380	1152
TTT GGA GCT GAT GAA ACT AAT GAT GAC AAC AAG GAA TAT GAT GCC TAT Phe Gly Ala Asp Glu Thr Asn Asp Asn Lys Glu Tyr Asp Ala Tyr 385 390 395 400	1200
CTC TCT TAC ACA AAA GTG GAC CAA GAT ACT TTA GAC TGT GAC AAT CCT Leu Ser Tyr Thr Lys Val Asp Gln Asp Thr Leu Asp Cys Asp Asn Pro 405 410 415	1248
GAA GAA GAG CAG TTT GCT CTT GAA GTA CTG CCA GAT GTC CTG GAA AAA Glu Glu Glu Gln Phe Ala Leu Glu Val Leu Pro Asp Val Leu Glu Lys 420 425 430	1296
CAC TAT GGA TAT AAA CTC TTC ATC CCA GAA AGA GAC CTG ATT CCA AGT His Tyr Gly Tyr Lys Leu Phe Ile Pro Glu Arg Asp Leu Ile Pro Ser 435 440 445	1344
GGA AGT GCA TAC ATG GAA GAT CTC ACA AGA TAT GTT GAA CAA AGC AGA Gly Ser Ala Tyr Met Glu Asp Leu Thr Arg Tyr Val Glu Gln Ser Arg 450 455 460	1392
AGA CTT ATT ATC GTG CTA ACT CCA GAC TAT ATT CTC AGA CGG GGA TGG Arg Leu Ile Ile Val Leu Thr Pro Asp Tyr Ile Leu Arg Arg Gly Trp 465 470 475 480	1440
AGT ATT TTC GAA CTG GAA AGC AGA CTC CAT AAC ATG CTA GTC AGT GGA Ser Ile Phe Glu Leu Glu Ser Arg Leu His Asn Met Leu Val Ser Gly 485 490 495	1488
GAA ATC AAA GTG ATT TTG ATT GAG TGT ACA GAA TTA AAA GGG AAA GTG Glu Ile Lys Val Ile Leu Ile Glu Cys Thr Glu Leu Lys Gly Lys Val 500 505 510	1536
AAT TGC CAG GAA GTG GAA TCA CTA AAG CGT AGC ATC AAA CTT CTG TCC Asn Cys Gln Glu Val Glu Ser Leu Lys Arg Ser Ile Lys Leu Leu Ser 515 520 525	1584
CTG ATC AAG TGG AAG GGA TCC AAA AGC AGC AAA TTA AAT TCT AAG TTT Leu Ile Lys Trp Lys Gly Ser Lys Ser Ser Lys Leu Asn Ser Lys Phe 530 535 540	1632

TGG AAG CAC TTA GTA TAT GAA ATG CCC ATC AAG AAA AAA GAA ATG CTA	1680
Trp Lys His Leu Val Tyr Glu Met Pro Ile Lys Lys Lys Glu Met Leu	
545 550 555 560	
CCT CGG TGC CAT GTT CTG GAC TCC GCA GAA CAA GGA CTT TTT GGA GAA	1728
Pro Arg Cys His Val Leu Asp Ser Ala Glu Gln Gly Leu Phe Gly Glu	
565 570 575 -	
CTC CAG CCT	1737
Leu Gln Pro	

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 579 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Leu	Leu	Leu	Thr	Leu	Leu	Val	Ser	Thr	Met	Leu	Thr	Val	Ser	Tyr	Thr
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Ser	Ser	Asp	Phe	Leu	Ser	Val	Asp	Gly	Cys	Ile	Asp	Trp	Ser	Val	Asp
				20				25					30		
Leu	Lys	Thr	Tyr	Met	Ala	Leu	Ala	Gly	Glu	Pro	Val	Arg	Val	Lys	Cys
				35			40						45		
Ala	Leu	Phe	Tyr	Ser	Tyr	Ile	Arg	Thr	Asn	Tyr	Ser	Thr	Ala	Gln	Ser
				50			55						60		
Thr	Gly	Leu	Arg	Leu	Met	Trp	Tyr	Lys	Asn	Lys	Gly	Asp	Leu	Glu	Glu
				65			70			75			80		
Pro	Ile	Ile	Phe	Ser	Glu	Val	Arg	Met	Ser	Lys	Glu	Glu	Asp	Ser	Ile
				85			90						95		
Trp	Phe	His	Ser	Ala	Glu	Ala	Gln	Asp	Ser	Gly	Phe	Tyr	Thr	Cys	Val
				100			105						110		
Leu	Arg	Asn	Ser	Thr	Tyr	Cys	Met	Lys	Val	Ser	Met	Ser	Leu	Thr	Val
				115			120						125		
Ala	Glu	Asn	Glu	Ser	Gly	Leu	Cys	Tyr	Asn	Ser	Arg	Ile	Arg	Tyr	Leu
				130			135			140					
Glu	Lys	Ser	Glu	Val	Thr	Lys	Arg	Lys	Glu	Ile	Ser	Cys	Pro	Asp	Met
				145			150			155			160		
Asp	Asp	Phe	Lys	Lys	Ser	Asp	Gln	Glu	Pro	Asp	Val	Val	Trp	Tyr	Lys
				165			170						175		
Glu	Cys	Lys	Pro	Lys	Met	Trp	Arg	Ser	Ile	Ile	Ile	Gln	Lys	Gly	Asn
				180			185						190		
Ala	Leu	Leu	Ile	Gln	Glu	Val	Gln	Glu	Glu	Asp	Gly	Gly	Asn	Tyr	Thr
				195			200						205		

Cys Glu Leu Lys Tyr Glu Gly Lys Leu Val Arg Arg Thr Thr Glu Leu
 210 215 220

Lys Val Thr Ala Leu Leu Thr Asp Lys Pro Pro Lys Pro Leu Phe Pro
 225 230 235 240

Met Glu Asn Gln Pro Ser Val Ile Asp Val Gln Leu Gly Lys Pro Leu
 245 250 255

Asn Ile Pro Cys Lys Ala Phe Phe Gly Phe Ser Gly Glu Ser Gly Pro
 260 265 270

Met Ile Tyr Trp Met Lys Gly Glu Lys Phe Ile Glu Glu Leu Ala Gly
 275 280 285

His Ile Arg Glu Gly Glu Ile Arg Leu Leu Lys Glu His Leu Gly Glu
 290 295 300

Lys Glu Val Glu Leu Ala Leu Ile Phe Asp Ser Val Val Glu Ala Asp
 305 310 315 320

Leu Ala Asn Tyr Thr Cys His Val Glu Asn Arg Asn Gly Arg Lys His
 325 330 335

Ala Ser Val Leu Leu Arg Lys Lys Asp Leu Ile Tyr Lys Ile Glu Leu
 340 345 350

Ala Gly Gly Leu Gly Ala Ile Phe Leu Leu Leu Val Leu Leu Val Val
 355 360 365

Ile Tyr Lys Cys Tyr Asn Ile Glu Leu Met Leu Phe Tyr Arg Gln His
 370 375 380

Phe Gly Ala Asp Glu Thr Asn Asp Asp Asn Lys Glu Tyr Asp Ala Tyr
 385 390 395 400

Leu Ser Tyr Thr Lys Val Asp Gln Asp Thr Leu Asp Cys Asp Asn Pro
 405 410 415

Glu Glu Glu Gln Phe Ala Leu Glu Val Leu Pro Asp Val Leu Glu Lys
 420 425 430

His Tyr Gly Tyr Lys Leu Phe Ile Pro Glu Arg Asp Leu Ile Pro Ser
 435 440 445

Gly Ser Ala Tyr Met Glu Asp Leu Thr Arg Tyr Val Glu Gln Ser Arg
 450 455 460

Arg Leu Ile Ile Val Leu Thr Pro Asp Tyr Ile Leu Arg Arg Gly Trp
 465 470 475 480

Ser Ile Phe Glu Leu Glu Ser Arg Leu His Asn Met Leu Val Ser Gly
 485 490 495

Glu Ile Lys Val Ile Leu Ile Glu Cys Thr Glu Leu Lys Gly Lys Val
 500 505 510

Asn Cys Gln Glu Val Glu Ser Leu Lys Arg Ser Ile Lys Leu Leu Ser
 515 520 525

Leu Ile Lys Trp Lys Gly Ser Lys Ser Ser Lys Leu Asn Ser Lys Phe
 530 535 540

Trp Lys His Leu Val Tyr Glu Met Pro Ile Lys Lys Lys Glu Met Leu
 545 550 555 560

Pro Arg Cys His Val Leu Asp Ser Ala Glu Gln Gly Leu Phe Gly Glu
 565 570 575

Leu Gln Pro

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2061 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..2058

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATG AAG CCA CCA TTT CTT TTG GCC CTT GTG GTC TGT TCT GTA GTC AGC	48
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ACA AAT CTG AAG ATG GTG TCA AAG AGA AAT TCT GTG GAT GGC TGC ATT	96
Thr Asn Leu Lys Met Val Ser Lys Arg Asn Ser Val Asp Gly Cys Ile	
20 25 30	
GAC TGG TCA GTG GAT CTC AAG ACA TAC ATG GCT TTG GCA GGT GAA CCA	144
Asp Trp Ser Val Asp Leu Lys Thr Tyr Met Ala Leu Ala Gly Glu Pro	
35 40 45	
GTC CGA GTG AAA TGT GCC CTT TTC TAC AGT TAT ATT CGT ACC AAC TAT	192
Val Arg Val Lys Cys Ala Leu Phe Tyr Ser Tyr Ile Arg Thr Asn Tyr	
50 55 60	
AGC ACG GCC CAG AGC ACT GGG CTC AGG CTT ATG TGG TAC AAA AAC AAA	240
Ser Thr Ala Gln Ser Thr Gly Leu Arg Leu Met Trp Tyr Lys Asn Lys	
65 70 75 80	
GGT GAT TTG GAA GAG CCC ATC ATC TTT TCA GAG GTC AGG ATG AGC AAA	288
Gly Asp Leu Glu Glu Pro Ile Ile Phe Ser Glu Val Arg Met Ser Lys	
85 90 95	
GAG GAA GAT TCA ATA TGG TTT CAC TCA GCT GAG GCA CAA GAC AGT GGA	336
Glu Glu Asp Ser Ile Trp Phe His Ser Ala Glu Ala Gln Asp Ser Gly	
100 105 110	
TTC TAC ACT TGT GTT TTA AGG AAC TCA ACA TAT TGC ATG AAG GTG TCA	384
Phe Tyr Thr Cys Val Leu Arg Asn Ser Thr Tyr Cys Met Lys Val Ser	
115 120 125	
ATG TCC TTG ACT GTT GCA GAG AAT GAA TCA GGC CTG TGC TAC AAC AGC	432
Met Ser Leu Thr Val Ala Glu Asn Glu Ser Gly Leu Cys Tyr Asn Ser	
130 135 140	

AGG ATC CGC TAT TTA GAA AAA TCT GAA GTC ACT AAA AGA AAG GAG ATC Arg Ile Arg Tyr Leu Glu Lys Ser Glu Val Thr Lys Arg Lys Glu Ile 145 150 155 160	480
TCC TGT CCA GAC ATG GAT GAC TTT AAA AAG TCC GAT CAG GAG CCT GAT Ser Cys Pro Asp Met Asp Asp Phe Lys Lys Ser Asp Gln Glu Pro Asp 165 170 175	528
GTT GTG TGG TAT AAG GAA TGC AAG CCA AAA ATG TGG AGA AGC ATA ATA Val Val Trp Tyr Lys Glu Cys Lys Pro Lys Met Trp Arg Ser Ile Ile 180 185 190	576
ATA CAG AAA GGA AAT GCT CTT CTG ATC CAA GAA GTT CAA GAA GAA GAT Ile Gln Lys Gly Asn Ala Leu Leu Ile Gln Glu Val Gln Glu Glu Asp 195 200 205	624
GGA GGA AAT TAC ACA TGT GAA CTT AAA TAT GAA GGA AAA CTT GTA AGA Gly Gly Asn Tyr Thr Cys Glu Leu Lys Tyr Glu Gly Lys Leu Val Arg 210 215 220	672
CGA ACA ACT GAA TTG AAA GTT ACA GCT TTA CTC ACA GAC AAG CCT CCC Arg Thr Thr Glu Leu Lys Val Thr Ala Leu Leu Thr Asp Lys Pro Pro 225 230 235 240	720
AAG CCA TTG TTC CCC ATG GAG AAT CAG CCA AGT GTT ATA GAT GTC CAG Lys Pro Leu Phe Pro Met Glu Asn Gln Pro Ser Val Ile Asp Val Gln 245 250 255	768
CTG GGT AAG CCT CTG AAC ATC CCC TGC AAA GCA TTC TTC GGA TTC AGT Leu Gly Lys Pro Leu Asn Ile Pro Cys Lys Ala Phe Phe Gly Phe Ser 260 265 270	816
GGA GAG TCT GGG CCA ATG ATC TAC TGG ATG AAA GGA GAA AAG TTT ATT Gly Glu Ser Gly Pro Met Ile Tyr Trp Met Lys Gly Glu Lys Phe Ile 275 280 285	864
GAA GAA CTG GCA GGT CAC ATT AGA GAA GGT GAA ATA AGG CTT CTC AAA Glu Glu Leu Ala Gly His Ile Arg Glu Gly Glu Ile Arg Leu Leu Lys 290 295 300	912
GAG CAT CTT GGA GAA AAA GAA GTT GAA TTG GCA CTC ATC TTT GAC TCA Glu His Leu Gly Glu Lys Glu Val Glu Leu Ala Leu Ile Phe Asp Ser 305 310 315 320	960
GTT GTG GAA GCT GAC CTG GCG AAT TAT ACC TGC CAT GTT GAA AAC CGA Val Val Glu Ala Asp Leu Ala Asn Tyr Thr Cys His Val Glu Asn Arg 325 330 335	1008
AAT GGA CGG AAA CAT GCC AGT GTT TTG CTG CGT AAA AAG GAT TTA ATC Asn Gly Arg Lys His Ala Ser Val Leu Leu Arg Lys Lys Asp Leu Ile 340 345 350	1056
TAT AAA ATT GAG CTT GCA GGG GGC CTG GGA GCA ATC TTC CTC CTC CTT Tyr Lys Ile Glu Leu Ala Gly Gly Leu Gly Ala Ile Phe Leu Leu Leu 355 360 365	1104
GTA CTG CTG GTG GTC ATT TAC AAA TGC TAC AAC ATT GAA TTG ATG CTC Val Leu Leu Val Val Ile Tyr Lys Cys Tyr Asn Ile Glu Leu Met Leu 370 375 380	1152
TTC TAC AGG CAG CAC TTT GGA GCT GAT GAA ACT AAT GAT GAC AAC AAG Phe Tyr Arg Gln His Phe Gly Ala Asp Glu Thr Asn Asp Asp Asn Lys 385 390 395 400	1200

GAA TAT GAT GCC TAT CTC TCT TAC ACA AAA GTG GAC CAA GAT ACT TTA Glu Tyr Asp Ala Tyr Leu Ser Tyr Thr Lys Val Asp Gln Asp Thr Leu 405 410 415	1248
GAC TGT GAC AAT CCT GAA GAA GAG CAG TTT GCT CTT GAA GTA CTG CCA Asp Cys Asp Asn Pro Glu Glu Glu Gln Phe Ala Leu Glu Val Leu Pro 420 425 430	1296
GAT GTC CTG GAA AAA CAC TAT GGA TAT AAA CTC TTC ATC CCA GAA AGA Asp Val Leu Glu Lys His Tyr Gly Tyr Lys Leu Phe Ile Pro Glu Arg 435 440 445	1344
GAC CTG ATT CCA AGT GGA ACA TAC ATG GAA GAT CTC ACA AGA TAT GTT Asp Leu Ile Pro Ser Gly Thr Tyr Met Glu Asp Leu Thr Arg Tyr Val 450 455 460	1392
GAA CAA AGC AGA AGA CTT ATT ATC GTG CTA ACT CCA GAC TAT ATT CTC Glu Gln Ser Arg Arg Leu Ile Ile Val Leu Thr Pro Asp Tyr Ile Leu 465 470 475 480	1440
AGA CGG GGA TGG AGT ATT TTC GAA CTG GAA AGC AGA CTC CAT AAC ATG Arg Arg Gly Trp Ser Ile Phe Glu Leu Glu Ser Arg Leu His Asn Met 485 490 495	1488
CTA GTC AGT GGA GAA ATC AAA GTG ATT TTG ATT GAG TGT ACA GAA TTA Leu Val Ser Gly Glu Ile Lys Val Ile Leu Ile Glu Cys Thr Glu Leu 500 505 510	1536
AAA GGG AAA GTG AAT TGC CAG GAA GTG GAA TCA CTA AAG CGT AGC ATC Lys Gly Lys Val Asn Cys Gln Glu Val Glu Ser Leu Lys Arg Ser Ile 515 520 525	1584
AAA CTT CTG TCC CTG ATC AAG TGG AAG GGA TCC AAA AGC AGC AAA TTA Lys Leu Leu Ser Leu Ile Lys Trp Lys Gly Ser Lys Ser Lys Leu 530 535 540	1632
AAT TCT AAG TTT TGG AAG CAC TTA GTA TAT GAA ATG CCC ATC AAG AAA Asn Ser Lys Phe Trp Lys His Leu Val Tyr Glu Met Pro Ile Lys Lys 545 550 555 560	1680
AAA GAA ATG CTA CCT CGG TGC CAT GTT CTG GAC TCC GCA GAA CAA GGA Lys Glu Met Leu Pro Arg Cys His Val Leu Asp Ser Ala Glu Gln Gly 565 570 575	1728
CTT TTT GGA GAA CTC CAG CCT ATA CCC TCT ATT GCC ATG ACC AGT ACT Leu Phe Gly Glu Leu Gln Pro Ile Pro Ser Ile Ala Met Thr Ser Thr 580 585 590	1776
TCA GCC ACT CTG GTG TCA TCT CAG GCT GAT CTC CCT GAA TTC CAC CCT Ser Ala Thr Leu Val Ser Ser Gln Ala Asp Leu Pro Glu Phe His Pro 595 600 605	1824
TCA GAT TCA ATG CAA ATC AGG CAC TGT TGC AGA GGT TAT AAA CAT GAG Ser Asp Ser Met Gln Ile Arg His Cys Cys Arg Gly Tyr Lys His Glu 610 615 620	1872
ATA CCA GCC ACG ACC TTG CCA GTC CCT TCC TTA GGC AAC CAC CAT ACT Ile Pro Ala Thr Thr Leu Pro Val Pro Ser Leu Gly Asn His His Thr 625 630 635 640	1920
TAT TGT AAC CTG CCT CTG ACG CTA CTC AAC GGA CAG CTA CCC CTT AAT Tyr Cys Asn Leu Pro Leu Thr Leu Leu Asn Gly Gln Leu Pro Leu Asn 645 650 655	1968

AAC ACC CTG AAA GAT ACC CAG GAA TTT CAC AGG AAC AGT TCT TTG CTG	2016
Asn Thr Leu Lys Asp Thr Gln Glu Phe His Arg Asn Ser Ser Leu Leu	
660 665 670	
CCT TTA TCC TCC AAA GAG CTT AGC TTT ACC AGT GAT ATT TGG	2058
Pro Leu Ser Ser Lys Glu Leu Ser Phe Thr Ser Asp Ile Trp	
675 680 685	
TAG	
	2061

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 686 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Lys Pro Pro Phe Leu Leu Ala Leu Val Val Cys Ser Val Val Ser	
1 5 10 15	

Thr Asn Leu Lys Met Val Ser Lys Arg Asn Ser Val Asp Gly Cys Ile	
20 25 30	

Asp Trp Ser Val Asp Leu Lys Thr Tyr Met Ala Leu Ala Gly Glu Pro	
35 40 45	

Val Arg Val Lys Cys Ala Leu Phe Tyr Ser Tyr Ile Arg Thr Asn Tyr	
50 55 60	

Ser Thr Ala Gln Ser Thr Gly Leu Arg Leu Met Trp Tyr Lys Asn Lys	
65 70 75 80	

Gly Asp Leu Glu Glu Pro Ile Ile Phe Ser Glu Val Arg Met Ser Lys	
85 90 95	

Glu Glu Asp Ser Ile Trp Phe His Ser Ala Glu Ala Gln Asp Ser Gly	
100 105 110	

Phe Tyr Thr Cys Val Leu Arg Asn Ser Thr Tyr Cys Met Lys Val Ser	
115 120 125	

Met Ser Leu Thr Val Ala Glu Asn Glu Ser Gly Leu Cys Tyr Asn Ser	
130 135 140	

Arg Ile Arg Tyr Leu Glu Lys Ser Glu Val Thr Lys Arg Lys Glu Ile	
145 150 155 160	

Ser Cys Pro Asp Met Asp Asp Phe Lys Lys Ser Asp Gln Glu Pro Asp	
165 170 175	

Val Val Trp Tyr Lys Glu Cys Lys Pro Lys Met Trp Arg Ser Ile Ile	
180 185 190	

Ile Gln Lys Gly Asn Ala Leu Leu Ile Gln Glu Val Gln Glu Glu Asp	
195 200 205	

Gly Gly Asn Tyr Thr Cys Glu Leu Lys Tyr Glu Gly Lys Leu Val Arg	
210 215 220	

Arg Thr Thr Glu Leu Lys Val Thr Ala Leu Leu Thr Asp Lys Pro Pro
 225 230 235 240
 Lys Pro Leu Phe Pro Met Glu Asn Gln Pro Ser Val Ile Asp Val Gln
 245 250 255
 Leu Gly Lys Pro Leu Asn Ile Pro Cys Lys Ala Phe Phe Gly Phe Ser
 260 265 270
 Gly Glu Ser Gly Pro Met Ile Tyr Trp Met Lys Gly Glu Lys Phe Ile
 275 280 285
 Glu Glu Leu Ala Gly His Ile Arg Glu Gly Glu Ile Arg Leu Leu Lys
 290 295 300
 Glu His Leu Gly Glu Lys Glu Val Glu Leu Ala Leu Ile Phe Asp Ser
 305 310 315 320
 Val Val Glu Ala Asp Leu Ala Asn Tyr Thr Cys His Val Glu Asn Arg
 325 330 335
 Asn Gly Arg Lys His Ala Ser Val Leu Leu Arg Lys Lys Asp Leu Ile
 340 345 350
 Tyr Lys Ile Glu Leu Ala Gly Gly Leu Gly Ala Ile Phe Leu Leu Leu
 355 360 365
 Val Leu Leu Val Val Ile Tyr Lys Cys Tyr Asn Ile Glu Leu Met Leu
 370 375 380
 Phe Tyr Arg Gln His Phe Gly Ala Asp Glu Thr Asn Asp Asp Asn Lys
 385 390 395 400
 Glu Tyr Asp Ala Tyr Leu Ser Tyr Thr Lys Val Asp Gln Asp Thr Leu
 405 410 415
 Asp Cys Asp Asn Pro Glu Glu Gln Phe Ala Leu Glu Val Leu Pro
 420 425 430
 Asp Val Leu Glu Lys His Tyr Gly Tyr Lys Leu Phe Ile Pro Glu Arg
 435 440 445
 Asp Leu Ile Pro Ser Gly Thr Tyr Met Glu Asp Leu Thr Arg Tyr Val
 450 455 460
 Glu Gln Ser Arg Arg Leu Ile Ile Val Leu Thr Pro Asp Tyr Ile Leu
 465 470 475 480
 Arg Arg Gly Trp Ser Ile Phe Glu Leu Glu Ser Arg Leu His Asn Met
 485 490 495
 Leu Val Ser Gly Glu Ile Lys Val Ile Leu Ile Glu Cys Thr Glu Leu
 500 505 510
 Lys Gly Lys Val Asn Cys Gln Glu Val Glu Ser Leu Lys Arg Ser Ile
 515 520 525
 Lys Leu Leu Ser Leu Ile Lys Trp Lys Gly Ser Lys Ser Ser Lys Leu
 530 535 540
 Asn Ser Lys Phe Trp Lys His Leu Val Tyr Glu Met Pro Ile Lys Lys
 545 550 555 560

Lys Glu Met Leu Pro Arg Cys His Val Leu Asp Ser Ala Glu Gln Gly
 565 570 575

Leu Phe Gly Glu Leu Gln Pro Ile Pro Ser Ile Ala Met Thr Ser Thr
 580 585 590

Ser Ala Thr Leu Val Ser Ser Gln Ala Asp Leu Pro Glu Phe His Pro
 595 600 605

Ser Asp Ser Met Gln Ile Arg His Cys Cys Arg Gly Tyr Lys His Glu
 610 615 620

Ile Pro Ala Thr Thr Leu Pro Val Pro Ser Leu Gly Asn His His Thr
 625 630 635 640

Tyr Cys Asn Leu Pro Leu Thr Leu Leu Asn Gly Gln Leu Pro Leu Asn
 645 650 655

Asn Thr Leu Lys Asp Thr Gln Glu Phe His Arg Asn Ser Ser Leu Leu
 660 665 670

Pro Leu Ser Ser Lys Glu Leu Ser Phe Thr Ser Asp Ile Trp
 675 680 685

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 482 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..480

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 9
- (D) OTHER INFORMATION: /note= "residues 9, 459, 462, 469, and 474 are indicated as C; each may be A, C, G, or T"

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 246
- (D) OTHER INFORMATION: /note= "residue 246 indicated as C, may be C or G"

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 321
- (D) OTHER INFORMATION: /note= "residues 321, 335, 360, and 423 are indicated as C; each may be C or T"

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 426
- (D) OTHER INFORMATION: /note= "residue 426 indicated as C, may be A or C"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

AAA TAT GGC TAT AGC CTG TTT TTC CTT GAA AGA AAT GTG GCT CCA GGA	48
Lys Tyr Gly Tyr Ser Leu Phe Phe Leu Glu Arg Asn Val Ala Pro Gly	
1 5 10 15	
GGA GTG TAT GCA GAA GAC ATT GTA AGC ATT ATT AAG AGA AGC AGA AGA	96
Gly Val Tyr Ala Glu Asp Ile Val Ser Ile Ile Lys Arg Ser Arg Arg	
20 25 30	
GGA ATA TTT ATC TTA ACC CCC AAC TAT GTC AAT GGA CCC AGT ATC TTT	144
Gly Ile Phe Ile Leu Thr Pro Asn Tyr Val Asn Gly Pro Ser Ile Phe	
35 40 45	
GAA CTA CAA GCA GCA GTG AAT CTT GCC TTG GAT GAT CAA ACA CTG AAA	192
Glu Leu Gln Ala Ala Val Asn Leu Ala Leu Asp Asp Gln Thr Leu Lys	
50 55 60	
CTC ATT TTA ATT AAG TTC TGT TAC TTC CAA GAG CCA GAG TCT CTA CCT	240
Leu Ile Leu Ile Lys Phe Cys Tyr Phe Gln Glu Pro Glu Ser Leu Pro	
65 70 75 80	
CAT CTC GTG AAA AAA GCT CTC AGG GTT TTG CCC ACA GTT ACT TGG AGA	288
His Leu Val Lys Lys Ala Leu Arg Val Leu Pro Thr Val Thr Trp Arg	
85 90 95	
GGC TTA AAA TCA GTT CCT CCC AAT TCT AGG TTC TGG GCC AAA ATG CGC	336
Gly Leu Lys Ser Val Pro Pro Asn Ser Arg Phe Trp Ala Lys Met Arg	
100 105 110	
TAC CAC ATG CCT GTG AAA AAT CTC TCA GGG ATT CAC GTG GGA ACC AGC	384
Tyr His Met Pro Val Lys Asn Leu Ser Gly Ile His Val Gly Thr Ser	
115 120 125	
TCC AGA ATT ACC TCT AGG GAT TTT TTC AGT GGA AAG GAC TCC GTA GAA	432
Ser Arg Ile Thr Ser Arg Asp Phe Phe Ser Gly Lys Asp Ser Val Glu	
130 135 140	
CAG AAA CCA TGG GGA GGA GCT CCC AGC CTC AAG GGA CGG TGC AAT GAG	480
Gln Lys Pro Trp Gly Gly Ala Pro Ser Leu Lys Gly Arg Cys Asn Glu	
145 150 155 160	
CC	482

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 160 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Lys Tyr Gly Tyr Ser Leu Phe Phe Leu Glu Arg Asn Val Ala Pro Gly	
1 5 10 15	
Gly Val Tyr Ala Glu Asp Ile Val Ser Ile Ile Lys Arg Ser Arg Arg	
20 25 30	
Gly Ile Phe Ile Leu Thr Pro Asn Tyr Val Asn Gly Pro Ser Ile Phe	
35 40 45	

Glu Leu Gln Ala Ala Val Asn Leu Ala Leu Asp Asp Gln Thr Leu Lys
 50 55 60

Leu Ile Leu Ile Lys Phe Cys Tyr Phe Gln Glu Pro Glu Ser Leu Pro
 65 70 75 80

His Leu Val Lys Lys Ala Leu Arg Val Leu Pro Thr Val Thr Trp Arg
 85 90 95

Gly Leu Lys Ser Val Pro Pro Asn Ser Arg Phe Trp Ala Lys Met Arg
 100 105 110

Tyr His Met Pro Val Lys Asn Leu Ser Gly Ile His Val Gly Thr Ser
 115 120 125

Ser Arg Ile Thr Ser Arg Asp Phe Phe Ser Gly Lys Asp Ser Val Glu
 130 135 140

Gln Lys Pro Trp Gly Gly Ala Pro Ser Leu Lys Gly Arg Cys Asn Glu
 145 150 155 160

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1404 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1401

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TTT CCT AGG AGC CCC TAT GAT GTA GCC TGT TGT GTC AAG ATG ATT TTA Phe Pro Arg Ser Pro Tyr Asp Val Ala Cys Cys Val Lys Met Ile Leu	48
1 5 10 15	
GAA GTT AAG CCC CAG ACA AAT GCA TCC TGT GAG TAT TCC GCA TCA CAT Glu Val Lys Pro Gln Thr Asn Ala Ser Cys Glu Tyr Ser Ala Ser His	96
20 25 30	
AAG CAA GAC CTA CTT CTT GGG AGC ACT GGC TCT ATT TCT TGC CCC AGT Lys Gln Asp Leu Leu Leu Gly Ser Thr Gly Ser Ile Ser Cys Pro Ser	144
35 40 45	
CTC AGC TGC CAA AGT GAT GCA CAA AGT CCA GCG GTA ACC TGG TAC AAG Leu Ser Cys Gln Ser Asp Ala Gln Ser Pro Ala Val Thr Trp Tyr Lys	192
50 55 60	
AAT CGA AAA CTC CTC TCT GTG GAA AGG AGC AAC CGA ATC GTA GTG GAT Asn Gly Lys Leu Leu Ser Val Glu Arg Ser Asn Arg Ile Val Val Asp	240
65 70 75 80	
GAA GTT TAT GAC TAT CAC CAG GGC ACA TAT GTA TGT GAT TAC ACT CAG Glu Val Tyr Asp Tyr His Gln Gly Thr Tyr Val Cys Asp Tyr Thr Gln	288
85 90 95	

TCG GAT ACT GTG AGT TCG TGG ACA GTC AGA GCT GTT GTT CAA GTG AGA Ser Asp Thr Val Ser Ser Trp Thr Val Arg Ala Val Val Gln Val Arg 100 105 110	336
ACC ATT GTG GGA GAC ACT AAA CTC AAA CCA GAT ATT CTG GAT CCT GTC Thr Ile Val Gly Asp Thr Lys Leu Lys Pro Asp Ile Leu Asp Pro Val 115 120 125	384
GAG GAC ACA CTG GAA GTA GAA CTT GGA AAG CCT TTA ACT ATT AGC TGC Glu Asp Thr Leu Glu Val Glu Leu Gly Lys Pro Leu Thr Ile Ser Cys 130 135 140	432
AAA GCA CGA TTT GGC TTT GAA AGG GTC TTT AAC CCT GTC ATA AAA TGG Lys Ala Arg Phe Gly Phe Glu Arg Val Phe Asn Pro Val Ile Lys Trp 145 150 155 160	480
TAC ATC AAA GAT TCT GAC CTA GAG TGG GAA GTC TCA GTA CCT GAG GCG Tyr Ile Lys Asp Ser Asp Leu Glu Trp Glu Val Ser Val Pro Glu Ala 165 170 175	528
AAA AGT ATT AAA TCC ACT TTA AAG GAT GAA ATC ATT GAG CGT AAT ATC Lys Ser Ile Lys Ser Thr Leu Lys Asp Glu Ile Ile Glu Arg Asn Ile 180 185 190	576
ATC TTG GAA AAA GTC ACT CAG CGT GAT CTT CGC AGG AAG TTT GTT TGC Ile Leu Glu Lys Val Thr Gln Arg Asp Leu Arg Arg Lys Phe Val Cys 195 200 205	624
TTT GTC CAG AAC TCC ATT GGA AAC ACA ACC CAG TCC GTC CAA CTG AAA Phe Val Gln Asn Ser Ile Gly Asn Thr Thr Gln Ser Val Gln Leu Lys 210 215 220	672
GAA AAG AGA GGA GTG GTG CTC CTG TAC ATC CTG CTT GGC ACC ATC GGG Glu Lys Arg Gly Val Val Leu Leu Tyr Ile Leu Leu Gly Thr Ile Gly 225 230 235 240	720
ACC CTG GTG GCC GTG CTG GCG AGT GCC CTC CTC TAC AGG CAC TGG Thr Leu Val Ala Val Leu Ala Ala Ser Ala Leu Leu Tyr Arg His Trp 245 250 255	768
ATT GAA ATA GTG CTG CTG TAC CGG ACC TAC CAG AGC AAG GAT CAG ACG Ile Glu Ile Val Leu Leu Tyr Arg Thr Tyr Gln Ser Lys Asp Gln Thr 260 265 270	816
CTT GGG GAT AAA AAG GAT TTT GAT GCT TTC GTA TCC TAT GCA AAA TGG Leu Gly Asp Lys Lys Asp Phe Asp Ala Phe Val Ser Tyr Ala Lys Trp 275 280 285	864
AGC TCT TTT CCA AGT GAG GCC ACT TCA TCT CTG AGT GAA GAA CAC TTG Ser Ser Phe Pro Ser Glu Ala Thr Ser Ser Leu Ser Glu Glu His Leu 290 295 300	912
GCC CTG AGC CTA TTT CCT GAT GTT TTA GAA AAC AAA TAT GGA TAT AGC Ala Leu Ser Leu Phe Pro Asp Val Leu Glu Asn Lys Tyr Gly Tyr Ser 305 310 315 320	960
CTG TGT TTG CTT GAA AGA GAT GTG GCT CCA GGA GGA GTG TAT GCA GAA Leu Cys Leu Leu Glu Arg Asp Val Ala Pro Gly Gly Val Tyr Ala Glu 325 330 335	1008
GAC ATT GTG AGC ATT ATT AAG AGA AGC AGA GAG GTA ATA TTT ATC TTG Asp Ile Val Ser Ile Ile Lys Arg Ser Arg Glu Val Ile Phe Ile Leu 340 345 350	1056

AGC CCC AAC TAT GTC AAT GGA CCC AGT ATC TTT GAA CTA CAA GCA GCA Ser Pro Asn Tyr Val Asn Gly Pro Ser Ile Phe Glu Leu Gln Ala Ala 355 360 365	1104
G TG AAT CTT GCC TTG GAT GAT CAA ACA CTG AAA CTC ATT TTA ATT AAG Val Asn Leu Ala Leu Asp Asp Gln Thr Leu Lys Leu Ile Leu Ile Lys 370 375 380	1152
TTC TGT TAC TTC CAA GAG CCA GAG TCT CTA CCT CAT CTC GTG AAA AAA Phe Cys Tyr Phe Gln Glu Pro Glu Ser Leu Pro His Leu Val Lys Lys 385 390 395 400	1200
GCT CTC AGG GTT TTG CCC ACA GTT ACT TGG AGA GGC TTA AAA TCA GTT Ala Leu Arg Val Leu Pro Thr Val Thr Trp Arg Gly Leu Lys Ser Val 405 410 415	1248
CCT CCC AAT TCT AGG TTC TGG GCC AAA ATG CGC TAC CAC ATG CCT GTG Pro Pro Asn Ser Arg Phe Trp Ala Lys Met Arg Tyr His Met Pro Val 420 425 430	1296
AAA AAC TCT CAG GGA TTC ACG TGG AAC CAG CTC AGA ATT ACC TCT AGG Lys Asn Ser Gln Gly Phe Thr Trp Asn Gln Leu Arg Ile Thr Ser Arg 435 440 445	1344
ATT TTT CAG TGG AAA GGA CTC AGT AGA ACA GAA ACC ACT GGG GAG GAG Ile Phe Gln Trp Lys Gly Leu Ser Arg Thr Glu Thr Thr Gly Glu Glu 450 455 460	1392
CTC CCA GCC TAA Leu Pro Ala 465	1404

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 467 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Phe Pro Arg Ser Pro Tyr Asp Val Ala Cys Cys Val Lys Met Ile Leu 1 5 10 15
Glu Val Lys Pro Gln Thr Asn Ala Ser Cys Glu Tyr Ser Ala Ser His 20 25 30
Lys Gln Asp Leu Leu Gly Ser Thr Gly Ser Ile Ser Cys Pro Ser 35 40 45
Leu Ser Cys Gln Ser Asp Ala Gln Ser Pro Ala Val Thr Trp Tyr Lys 50 55 60
Asn Gly Lys Leu Leu Ser Val Glu Arg Ser Asn Arg Ile Val Val Asp 65 70 75 80
Glu Val Tyr Asp Tyr His Gln Gly Thr Tyr Val Cys Asp Tyr Thr Gln 85 90 95

Ser Asp Thr Val Ser Ser Trp Thr Val Arg Ala Val Val Gln Val Arg
 100 105 110

Thr Ile Val Gly Asp Thr Lys Leu Lys Pro Asp Ile Leu Asp Pro Val
 115 120 125

Glu Asp Thr Leu Glu Val Glu Leu Gly Lys Pro Leu Thr Ile Ser Cys
 130 135 140

Lys Ala Arg Phe Gly Phe Glu Arg Val Phe Asn Pro Val Ile Lys Trp
 145 150 155 160

Tyr Ile Lys Asp Ser Asp Leu Glu Trp Glu Val Ser Val Pro Glu Ala
 165 170 175

Lys Ser Ile Lys Ser Thr Leu Lys Asp Glu Ile Ile Glu Arg Asn Ile
 180 185 190

Ile Leu Glu Lys Val Thr Gln Arg Asp Leu Arg Arg Lys Phe Val Cys
 195 200 205

Phe Val Gln Asn Ser Ile Gly Asn Thr Thr Gln Ser Val Gln Leu Lys
 210 215 220

Glu Lys Arg Gly Val Val Leu Leu Tyr Ile Leu Leu Gly Thr Ile Gly
 225 230 235 240

Thr Leu Val Ala Val Leu Ala Ala Ser Ala Leu Leu Tyr Arg His Trp
 245 250 255

Ile Glu Ile Val Leu Leu Tyr Arg Thr Tyr Gln Ser Lys Asp Gln Thr
 260 265 270

Leu Gly Asp Lys Lys Asp Phe Asp Ala Phe Val Ser Tyr Ala Lys Trp
 275 280 285

Ser Ser Phe Pro Ser Glu Ala Thr Ser Ser Leu Ser Glu Glu His Leu
 290 295 300

Ala Leu Ser Leu Phe Pro Asp Val Leu Glu Asn Lys Tyr Gly Tyr Ser
 305 310 315 320

Leu Cys Leu Leu Glu Arg Asp Val Ala Pro Gly Gly Val Tyr Ala Glu
 325 330 335

Asp Ile Val Ser Ile Ile Lys Arg Ser Arg Glu Val Ile Phe Ile Leu
 340 345 350

Ser Pro Asn Tyr Val Asn Gly Pro Ser Ile Phe Glu Leu Gln Ala Ala
 355 360 365

Val Asn Leu Ala Leu Asp Asp Gln Thr Leu Lys Leu Ile Leu Ile Lys
 370 375 380

Phe Cys Tyr Phe Gln Glu Pro Glu Ser Leu Pro His Leu Val Lys Lys
 385 390 395 400

Ala Leu Arg Val Leu Pro Thr Val Thr Trp Arg Gly Leu Lys Ser Val
 405 410 415

Pro Pro Asn Ser Arg Phe Trp Ala Lys Met Arg Tyr His Met Pro Val
 420 425 430

Lys Asn Ser Gln Gly Phe Thr Trp Asn Gln Leu Arg Ile Thr Ser Arg
435 440 445

Ile Phe Gln Trp Lys Gly Leu Ser Arg Thr Glu Thr Thr Gly Glu Glu
 450 455 460

Leu Pro Ala
465

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2314 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 109..1905

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AAG AGC CCC TAT GAT GTA GCC TGT TGT GTC AAG ATG ATT TTA GAA GTT Lys Ser Pro Tyr Asp Val Ala Cys Cys Val Lys Met Ile Leu Glu Val 135 140 145	549
AAG CCC CAG ACA AAT GCA TCC TGT GAG TAT TCC GCA TCA CAT AAG CAA Lys Pro Gln Thr Asn Ala Ser Cys Glu Tyr Ser Ala Ser His Lys Gln 150 155 160	597
GAC CTA CTT CTT GGG AGC ACT GGC TCT ATT TCT TGC CCC AGT CTC AGC Asp Leu Leu Leu Gly Ser Thr Gly Ser Ile Ser Cys Pro Ser Leu Ser 165 170 175	645
TGC CAA AGT GAT GCA CAA AGT CCA GCG GTA ACC TGG TAC AAG AAT GGA Cys Gln Ser Asp Ala Gln Ser Pro Ala Val Thr Trp Tyr Lys Asn Gly 180 185 190 195	693
AAA CTC CTC TCT GTG GAA AGG AGC AAC CGA ATC GTA GTG GAT GAA GTT Lys Leu Leu Ser Val Glu Arg Ser Asn Arg Ile Val Val Asp Glu Val 200 205 210	741
TAT GAC TAT CAC CAG GGC ACA TAT GTA TGT GAT TAC ACT CAG TCG GAT Tyr Asp Tyr His Gln Gly Thr Tyr Val Cys Asp Tyr Thr Gln Ser Asp 215 220 225	789
ACT GTG AGT TCG TGG ACA GTC AGA GCT GTT GTT CAA GTG AGA ACC ATT Thr Val Ser Ser Trp Thr Val Arg Ala Val Val Gln Val Arg Thr Ile 230 235 240	837
GTG GGA GAC ACT AAA CTC AAA CCA GAT ATT CTG GAT CCT GTC GAG GAC Val Gly Asp Thr Lys Leu Lys Pro Asp Ile Leu Asp Pro Val Glu Asp 245 250 255	885
ACA CTG GAA GTA GAA CTT GGA AAG CCT TTA ACT ATT AGC TGC AAA GCA Thr Leu Glu Val Glu Leu Gly Lys Pro Leu Thr Ile Ser Cys Lys Ala 260 265 270 275	933
CGA TTT GGC TTT GAA AGG GTC TTT AAC CCT GTC ATA AAA TGG TAC ATC Arg Phe Gly Phe Glu Arg Val Phe Asn Pro Val Ile Lys Trp Tyr Ile 280 285 290	981
AAA GAT TCT GAC CTA GAG TGG GAA GTC TCA GTA CCT GAG GCG AAA AGT Lys Asp Ser Asp Leu Glu Trp Glu Val Ser Val Pro Glu Ala Lys Ser 295 300 305	1029
ATT AAA TCC ACT TTA AAG GAT GAA ATC ATT GAG CGT AAT ATC ATC TTG Ile Lys Ser Thr Leu Lys Asp Glu Ile Ile Glu Arg Asn Ile Ile Leu 310 315 320	1077
GAA AAA GTC ACT CAG CGT GAT CTT CGC AGG AAG TTT GTT TGC TTT GTC Glu Lys Val Thr Gln Arg Asp Leu Arg Arg Lys Phe Val Cys Phe Val 325 330 335	1125
CAG AAC TCC ATT GGA AAC ACA ACC CAG TCC GTC CAA CTG AAA GAA AAG Gln Asn Ser Ile Gly Asn Thr Thr Gln Ser Val Gln Leu Lys Glu Lys 340 345 350 355	1173
AGA GGA GTG GTG CTC CTG TAC ATC CTG CTT GGC ACC ATC GGG ACC CTG Arg Gly Val Val Leu Leu Tyr Ile Leu Leu Gly Thr Ile Gly Thr Leu 360 365 370	1221
GTG GCC GTG CTG GCG GCG AGT GCC CTC CTC TAC AGG CAC TGG ATT GAA Val Ala Val Leu Ala Ala Ser Ala Leu Leu Tyr Arg His Trp Ile Glu 375 380 385	1269

ATA GTG CTG CTG TAC CGG ACC TAC CAG AGC AAG GAT CAG ACG CTT GGG Ile Val Leu Leu Tyr Arg Thr Tyr Gln Ser Lys Asp Gln Thr Leu Gly 390 395 400	1317
GAT AAA AAG GAT TTT GAT GCT TTC GTA TCC TAT GCA AAA TGG AGC TCT Asp Lys Lys Asp Phe Asp Ala Phe Val Ser Tyr Ala Lys Trp Ser Ser 405 410 415	1365
TTT CCA AGT GAG GCC ACT TCA TCT CTG AGT GAA GAA CAC TTG GCC CTG Phe Pro Ser Glu Ala Thr Ser Ser Leu Ser Glu Glu His Leu Ala Leu 420 425 430 435	1413
AGC CTA TTT CCT GAT GTT TTA GAA AAC AAA TAT GGA TAT AGC CTG TGT Ser Leu Phe Pro Asp Val Leu Glu Asn Lys Tyr Gly Tyr Ser Leu Cys 440 445 450	1461
TTG CTT GAA AGA GAT GTG GCT CCA GGA GGA GTG TAT GCA GAA GAC ATT Leu Leu Glu Arg Asp Val Ala Pro Gly Gly Val Tyr Ala Glu Asp Ile 455 460 465	1509
GTG AGC ATT ATT AAG AGA AGC AGA AGA GGA ATA TTT ATC TTG AGC CCC Val Ser Ile Ile Lys Arg Ser Arg Arg Gly Ile Phe Ile Leu Ser Pro 470 475 480	1557
AAC TAT GTC AAT GGA CCC AGT ATC TTT GAA CTA CAA GCA GCA GTG AAT Asn Tyr Val Asn Gly Pro Ser Ile Phe Glu Leu Gln Ala Ala Val Asn 485 490 495	1605
CTT GCC TTG GAT GAT CAA ACA CTC ATT TTA ATT AAG TTC TGT Leu Ala Leu Asp Asp Gln Thr Leu Lys Leu Ile Leu Ile Lys Phe Cys 500 505 510 515	1653
TAC TTC CAA GAG CCA GAG TCT CTA CCT CAT CTC GTG AAA AAA GCT CTC Tyr Phe Gln Glu Pro Glu Ser Leu Pro His Leu Val Lys Lys Ala Leu 520 525 530	1701
AGG GTT TTG CCC ACA GTT ACT TGG AGA GGC TTA AAA TCA GTT CCT CCC Arg Val Leu Pro Thr Val Thr Trp Arg Gly Leu Lys Ser Val Pro Pro 535 540 545	1749
AAT TCT AGG TTC TGG GCC AAA ATG CGC TAC CAC ATG CCT GTG AAA AAC Asn Ser Arg Phe Trp Ala Lys Met Arg Tyr His Met Pro Val Lys Asn 550 555 560	1797
TCT CAG GGA TTC ACG TGG AAC CAG CTC AGA ATT ACC TCT AGG ATT TTT Ser Gln Gly Phe Thr Trp Asn Gln Leu Arg Ile Thr Ser Arg Ile Phe 565 570 575	1845
CAG TGG AAA GGA CTC AGT AGA ACA GAA ACC ACT GGG AGG AGC TCC CAG Gln Trp Lys Gly Leu Ser Arg Thr Glu Thr Thr Gly Arg Ser Ser Gln 580 585 590 595	1893
CCT AAG GAA TGG TGAAATGAGC CCTGGAGCCC CCTCCAGTCC AGTCCCTGGG Pro Lys Glu Trp	1945
ATAGAGATGT TGCTGGACAG AACTCACAGC TCTGTGTGTG TGTGTTCAAGG CTGATAGGAA	2005
ATTCAAAGAG TCTCCTGCCA GCACCAAGCA AGCTTGATGG ACAATGGAAT GGGATTGAGA	2065
CTGTGGTTA GAGCCCTTGA TTTCTGGAC TGGACAGACG GCGAGTGAAT TCTCTAGACC	2125
TTGGGTACTT TCAGTACACA ACACCCCTAA GATTCCCAG TGGTCCGAGC AGAACATCAGAA	2185

AATAACAGCTA CTTCTGCCTT ATGGCTAGGG AACTGTCATG TCTACCATGT ATTGTACATA	2245
TGACTTTATG TATACTTGCA ATCAAATAAA TATTATTTTA TTAGAAAAAA AAAAAAAAAG	2305
GGCGGGCCGC	2314

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 599 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Met Leu Cys Leu Gly Trp Ile Phe Leu Trp Leu Val Ala Gly Glu Arg	
1 5 10 15	
Ile Lys Gly Phe Asn Ile Ser Gly Cys Ser Thr Lys Lys Leu Leu Trp	
20 25 30	
Thr Tyr Ser Thr Arg Ser Glu Glu Glu Phe Val Leu Phe Cys Asp Leu	
35 40 45	
Pro Glu Pro Gln Lys Ser His Phe Cys His Arg Asn Arg Leu Ser Pro	
50 55 60	
Lys Gln Val Pro Glu His Leu Pro Phe Met Gly Ser Asn Asp Leu Ser	
65 70 75 80	
Asp Val Gln Trp Tyr Gln Gln Pro Ser Asn Gly Asp Pro Leu Glu Asp	
85 90 95	
Ile Arg Lys Ser Tyr Pro His Ile Ile Gln Asp Lys Cys Thr Leu His	
100 105 110	
Phe Leu Thr Pro Gly Val Asn Asn Ser Gly Ser Tyr Ile Cys Arg Pro	
115 120 125	
Lys Met Ile Lys Ser Pro Tyr Asp Val Ala Cys Cys Val Lys Met Ile	
130 135 140	
Leu Glu Val Lys Pro Gln Thr Asn Ala Ser Cys Glu Tyr Ser Ala Ser	
145 150 155 160	
His Lys Gln Asp Leu Leu Leu Gly Ser Thr Gly Ser Ile Ser Cys Pro	
165 170 175	
Ser Leu Ser Cys Gln Ser Asp Ala Gln Ser Pro Ala Val Thr Trp Tyr	
180 185 190	
Lys Asn Gly Lys Leu Leu Ser Val Glu Arg Ser Asn Arg Ile Val Val	
195 200 205	
Asp Glu Val Tyr Asp Tyr His Gln Gly Thr Tyr Val Cys Asp Tyr Thr	
210 215 220	
Gln Ser Asp Thr Val Ser Ser Trp Thr Val Arg Ala Val Val Gln Val	
225 230 235 240	

Arg Thr Ile Val Gly Asp Thr Lys Leu Lys Pro Asp Ile Leu Asp Pro
 245 250 255
 Val Glu Asp Thr Leu Glu Val Glu Leu Gly Lys Pro Leu Thr Ile Ser
 260 265 270
 Cys Lys Ala Arg Phe Gly Phe Glu Arg Val Phe Asn Pro Val Ile Lys
 275 280 285
 Trp Tyr Ile Lys Asp Ser Asp Leu Glu Trp Glu Val Ser Val Pro Glu
 290 295 300
 Ala Lys Ser Ile Lys Ser Thr Leu Lys Asp Glu Ile Ile Glu Arg Asn
 305 310 315 320
 Ile Ile Leu Glu Lys Val Thr Gln Arg Asp Leu Arg Arg Lys Phe Val
 325 330 335
 Cys Phe Val Gln Asn Ser Ile Gly Asn Thr Thr Gln Ser Val Gln Leu
 340 345 350
 Lys Glu Lys Arg Gly Val Val Leu Leu Tyr Ile Leu Leu Gly Thr Ile
 355 360 365
 Gly Thr Leu Val Ala Val Ala Ala Ser Ala Leu Leu Tyr Arg His
 370 375 380
 Trp Ile Glu Ile Val Leu Leu Tyr Arg Thr Tyr Gln Ser Lys Asp Gln
 385 390 395 400
 Thr Leu Gly Asp Lys Lys Asp Phe Asp Ala Phe Val Ser Tyr Ala Lys
 405 410 415
 Trp Ser Ser Phe Pro Ser Glu Ala Thr Ser Ser Leu Ser Glu Glu His
 420 425 430
 Leu Ala Leu Ser Leu Phe Pro Asp Val Leu Glu Asn Lys Tyr Gly Tyr
 435 440 445
 Ser Leu Cys Leu Leu Glu Arg Asp Val Ala Pro Gly Gly Val Tyr Ala
 450 455 460
 Glu Asp Ile Val Ser Ile Ile Lys Arg Ser Arg Arg Gly Ile Phe Ile
 465 470 475 480
 Leu Ser Pro Asn Tyr Val Asn Gly Pro Ser Ile Phe Glu Leu Gln Ala
 485 490 495
 Ala Val Asn Leu Ala Leu Asp Asp Gln Thr Leu Lys Leu Ile Leu Ile
 500 505 510
 Lys Phe Cys Tyr Phe Gln Glu Pro Glu Ser Leu Pro His Leu Val Lys
 515 520 525
 Lys Ala Leu Arg Val Leu Pro Thr Val Thr Trp Arg Gly Leu Lys Ser
 530 535 540
 Val Pro Pro Asn Ser Arg Phe Trp Ala Lys Met Arg Tyr His Met Pro
 545 550 555 560
 Val Lys Asn Ser Gln Gly Phe Thr Trp Asn Gln Leu Arg Ile Thr Ser
 565 570 575

Arg Ile Phe Gln Trp Lys Gly Leu Ser Arg Thr Glu Thr Thr Gly Arg
 580 585 590

Ser Ser Gln Pro Lys Glu Trp
 595

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 768 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 1..360

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GCA GCA GTG AAT CTT GCC TTG GTT GAT CAG ACA CTG AAG TTG ATT TTA Ala Ala Val Asn Leu Ala Leu Val Asp Gln Thr Leu Lys Leu Ile Leu 1 5 10 15	48
ATT AAG TTC TGT TCC TTC CAA GAG CCA GAA TCT CTT CCT TAC CTT GTC Ile Lys Phe Cys Ser Phe Gln Glu Pro Glu Ser Leu Pro Tyr Leu Val 20 25 30	96
AAA AAG GCT CTG CGG GTT CTC CCC ACA GTC ACA TGG AAA GGC TTG AAG Lys Lys Ala Leu Arg Val Leu Pro Thr Val Thr Trp Lys Gly Leu Lys 35 40 45	144
TCG GTC CAC GCC AGT TCC AGG TTC TGG ACC CAA ATT CGT TAC CAC ATG Ser Val His Ala Ser Ser Arg Phe Trp Thr Gln Ile Arg Tyr His Met 50 55 60	192
CCT GTG AAG AAC TCC AAC AGG TTT ATG TTC AAC GGG CTC AGA ATT TTC Pro Val Lys Asn Ser Asn Arg Phe Met Phe Asn Gly Leu Arg Ile Phe 65 70 75 80	240
CTG AAG GGC TTT TCC CCT GAA AAG GAC CTA GTG ACA CAG AAA CCC CTG Leu Lys Gly Phe Ser Pro Glu Lys Asp Leu Val Thr Gln Lys Pro Leu 85 90 95	288
GAA GGA ATG CCC AAG TCT GGG AAT GAC CAC GGA GCT CAG AAC CTC CTT Glu Gly Met Pro Lys Ser Gly Asn Asp His Gly Ala Gln Asn Leu Leu 100 105 110	336
CTC TAC AGT GAC CAG AAG AGG TGC TGATGGGTAG AACTTGCTGT GTGGATCAGG Leu Tyr Ser Asp Gln Lys Arg Cys 115 120	390
CTGATAGAAA TTGAGCCTTT CTGCTCTCAG TGCCAAGCAA GCTTGACAGG CAGTGGAAATG AAGCGGCATC TGTGGTTTA GGGTCTGGGT TCCTGGAACA GACACAGAGC AATACTCCAG ACCTCTGCCG TGTGCTTAGC ACACATTCC CTGAGAGTTC CCAAGTAGCC TGAACAGAAT CAACAGAAAT AGCTCCATGG GCTGTCCAAC ATTCAATGCAC GCATGCCTGT TTTGCACTAT	450 510 570 630

ATATATGAAT TTATCATACG TTTGTGTGTG TATATGCATT CAGATAAATA GGATTTATT	690
TTGTTCGATA CGAGTGATTG AAACTCCATT TAAAGCCCTT CTGTAAAGAA ATTTTGCTGC	750
AAAAAAAAA AAAAAAAA	768

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 120 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Ala Ala Val Asn Leu Ala Leu Val Asp Gln Thr Leu Lys Leu Ile Leu			
1	5	10	15
Ile Lys Phe Cys Ser Phe Gln Glu Pro Glu Ser Leu Pro Tyr Leu Val			
20	25	30	
Lys Lys Ala Leu Arg Val Leu Pro Thr Val Thr Trp Lys Gly Leu Lys			
35	40	45	
Ser Val His Ala Ser Ser Arg Phe Trp Thr Gln Ile Arg Tyr His Met			
50	55	60	
Pro Val Lys Asn Ser Asn Arg Phe Met Phe Asn Gly Leu Arg Ile Phe			
65	70	75	80
Leu Lys Gly Phe Ser Pro Glu Lys Asp Leu Val Thr Gln Lys Pro Leu			
85	90	95	
Glu Gly Met Pro Lys Ser Gly Asn Asp His Gly Ala Gln Asn Leu Leu			
100	105	110	
Leu Tyr Ser Asp Gln Lys Arg Cys			
115	120		

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1833 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1830

(ix) FEATURE:

- (A) NAME/KEY: mat_peptide
- (B) LOCATION: 52..1830

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

ATG TCT GTT TGG CTG GTG TTC TTG GTT TGT GCA GGA GAG AAG ACC ACA Met Ser Val Trp Leu Val Phe Leu Val Cys Ala Gly Glu Lys Thr Thr -17 -15 -10 -5	48
GGA TTT AAT CAT TCA GCT TGT GCC ACC AAA AAT TCT GTG GAC ATA TTC Gly Phe Asn His Ser Ala Cys Ala Thr Lys Asn Ser Val Asp Ile Phe 1 5 10 ~15	96
GCA AGG GGT GCA GAG AAT TTT GTC TAT TTT GTG ACT TAC AAG AGC TTC Ala Arg Gly Ala Glu Asn Phe Val Tyr Phe Val Thr Tyr Lys Ser Phe 20 25 30	144
AGG AGC AAA AAT TCT CCC ATG CAA GTC AAC TGT CAC CAA CAC AAA GTC Arg Ser Lys Asn Ser Pro Met Gln Val Asn Cys His Gln His Lys Val 35 40 45	192
TGC TCA CAA ACT TGC AGT GGC AGT CAG AAG GAC TTA TCT GAT GTC CAG Cys Ser Gln Thr Cys Ser Gly Ser Gln Lys Asp Leu Ser Asp Val Gln 50 55 60	240
TGG TAC ATG CAA CCT CGG AGT GGA AGT CCA CTA GAG GAG ATC AGT AGA Trp Tyr Met Gln Pro Arg Ser Gly Ser Pro Leu Glu Glu Ile Ser Arg 65 70 75	288
AAC TCT CCC CAT ATG CAG AGT GAA GGC ATG CTG CAT ATA TTG GCC CCA Asn Ser Pro His Met Gln Ser Glu Gly Met Leu His Ile Leu Ala Pro 80 85 90 95	336
CAG ACG AAC AGC ATT TGG TCA TAT ATT TGT AGA CCC AGA ATT AGG AGC Gln Thr Asn Ser Ile Trp Ser Tyr Ile Cys Arg Pro Arg Ile Arg Ser 100 105 110	384
CCC CAG GAT ATG GCC TGT TGT ATC AAG ACA GTC TTA GAA GTT AAG CCT Pro Gln Asp Met Ala Cys Cys Ile Lys Thr Val Leu Glu Val Lys Pro 115 120 125	432
CAG AGA AAC GTG TCC TGT GGG AAC ACA GCA CAA GAT GAA CAA GTC CTA Gln Arg Asn Val Ser Cys Gly Asn Thr Ala Gln Asp Glu Gln Val Leu 130 135 140	480
CTT CTT GGC AGT ACT GGC TCC ATT CAT TGT CCC AGT CTC AGC TGC CAA Leu Leu Gly Ser Thr Gly Ser Ile His Cys Pro Ser Leu Ser Cys Gln 145 150 155	528
AGT GAT GTA CAG AGT CCA GAG ATG ACC TGG TAC AAG GAT GGA AGA CTA Ser Asp Val Gln Ser Pro Glu Met Thr Trp Tyr Lys Asp Gly Arg Leu 160 165 170 175	576
CTT CCT GAG CAC AAG AAA AAT CCA ATT GAG ATG GCA GAT ATT TAT GTT Leu Pro Glu His Lys Lys Asn Pro Ile Glu Met Ala Asp Ile Tyr Val 180 185 190	624
TTT AAT CAA GGC TTG TAT GTA TGT GAT TAC ACA CAG TCA GAT AAT GTG Phe Asn Gln Gly Leu Tyr Val Cys Asp Tyr Thr Gln Ser Asp Asn Val 195 200 205	672
AGT TCC TGG ACA GTC CGA GCT GTG GTT AAA GTG AGA ACC ATT GGT AAG Ser Ser Trp Thr Val Arg Ala Val Val Lys Val Arg Thr Ile Gly Lys 210 215 220	720
GAC ATC AAT GTG AAG CCG GAA ATT CTG GAT CCC ATT ACA GAT ACA CTG Asp Ile Asn Val Lys Pro Glu Ile Leu Asp Pro Ile Thr Asp Thr Leu 225 230 235	768

GAC GTA GAG CTT GGA AAG CCT TTA ACT CTC CCC TGC AGA GTA CAG TTT Asp Val Glu Leu Gly Lys Pro Leu Thr Leu Pro Cys Arg Val Gln Phe 240 245 250 255	816
GGC TTC CAA AGA CTT TCA AAG CCT GTG ATA AAG TGG TAT GTC AAA GAA Gly Phe Gln Arg Leu Ser Lys Pro Val Ile Lys Trp Tyr Val Lys Glu 260 265 270	864
TCT ACA CAG GAG TGG GAA ATG TCA GTA TTT GAG GAG AAA AGA ATT CAA Ser Thr Gln Glu Trp Glu Met Ser Val Phe Glu Glu Lys Arg Ile Gln 275 280 285	912
TCC ACT TTC AAG AAT GAA GTC ATT GAA CGT ACC ATC TTC TTG AGA GAA Ser Thr Phe Lys Asn Glu Val Ile Glu Arg Thr Ile Phe Leu Arg Glu 290 295 300	960
GTT ACC CAG AGA GAT CTC AGC AGA AAG TTT GTT TGC TTT GCC CAG AAC Val Thr Gln Arg Asp Leu Ser Arg Lys Phe Val Cys Phe Ala Gln Asn 305 310 315	1008
TCC ATT GGG AAC ACA ACA CGG ACC ATA CGG CTG AGG AAG AAG GAA GAG Ser Ile Gly Asn Thr Thr Arg Thr Ile Arg Leu Arg Lys Lys Glu Glu 320 325 330 335	1056
G TG GTG TTT GTA TAC ATC CTT CTC GGC ACG GCC TTG ATG CTG GTG GGC Val Val Phe Val Tyr Ile Leu Leu Gly Thr Ala Leu Met Leu Val Gly 340 345 350	1104
GTT CTG GTG GCA GCT GCT TTC CTC TAC TGG TAC TGG ATT GAA GTT GTC Val Leu Val Ala Ala Phe Leu Tyr Trp Tyr Trp Ile Glu Val Val 355 360 365	1152
CTG CTC TGT CGA ACC TAC AAG AAC AAA GAT GAG ACT CTG GGG GAT AAG Leu Leu Cys Arg Thr Tyr Lys Asn Lys Asp Glu Thr Leu Gly Asp Lys 370 375 380	1200
AAG GAA TTC GAT GCA TTT GTA TCC TAC TCG AAT TGG AGC TCT CCT GAG Lys Glu Phe Asp Ala Phe Val Ser Tyr Ser Asn Trp Ser Ser Pro Glu 385 390 395	1248
ACT GAC GCC GTG GGA TCT CTG AGT GAG GAA CAC CTG GCT CTG AAT CTT Thr Asp Ala Val Gly Ser Leu Ser Glu Glu His Leu Ala Leu Asn Leu 400 405 410 415	1296
TTC CCG GAA GTG CTA GAA GAC ACC TAT GGG TAC AGA TTG TGT TTG CTT Phe Pro Glu Val Leu Glu Asp Thr Tyr Gly Tyr Arg Leu Cys Leu Leu 420 425 430	1344
GAC CGA GAT GTG ACC CCA GGA GGA GTG TAT GCA GAT GAC ATT GTG AGC Asp Arg Asp Val Thr Pro Gly Gly Val Tyr Ala Asp Asp Ile Val Ser 435 440 445	1392
ATC ATT AAG AAA AGC CGA AGA GGA ATA TTT ATC CTG AGT CCC AGC TAC Ile Ile Lys Lys Ser Arg Arg Gly Ile Phe Ile Leu Ser Pro Ser Tyr 450 455 460	1440
CTC AAT GGA CCC CGT GTC TTT GAG CTA CAA GCA GCA GTG AAT CTT GCC Leu Asn Gly Pro Arg Val Phe Glu Leu Gln Ala Ala Val Asn Leu Ala 465 470 475	1488
TTG GTT GAT CAG ACA CTG AAG TTG ATT TTA ATT AAG TTC TGT TCC TTC Leu Val Asp Gln Thr Leu Lys Leu Ile Leu Ile Lys Phe Cys Ser Phe 480 485 490 495	1536

CAA GAG CCA GAA TCT CTT CCT TAC CTT GTC AAA AAG GCT CTG CGG GTT	500	505	510	1584
Gln Glu Pro Glu Ser Leu Pro Tyr Leu Val Lys Lys Ala Leu Arg Val				
CTC CCC ACA GTC ACA TGG AAA GGC TTG AAG TCG GTC CAC GCC AGT TCC	515	520	525	1632
Leu Pro Thr Val Thr Trp Lys Gly Leu Lys Ser Val His Ala Ser Ser				
AGG TTC TGG ACC CAA ATT CGT TAC CAC ATG CCT GTG AAG AAC TCC AAC	530	535	540	1680
Arg Phe Trp Thr Gln Ile Arg Tyr His Met Pro Val Lys Asn Ser Asn				
AGG TTT ATG TTC AAC GGG CTC AGA ATT TTC CTG AAG GGC TTT TCC CCT	545	550	555	1728
Arg Phe Met Phe Asn Gly Leu Arg Ile Phe Leu Lys Gly Phe Ser Pro				
GAA AAG GAC CTA GTG ACA CAG AAA CCC CTG GAA GGA ATG CCC AAG TCT	560	565	570	1776
Glu Lys Asp Leu Val Thr Gln Lys Pro Leu Glu Gly Met Pro Lys Ser				
GGG AAT GAC CAC GGA GCT CAG AAC CTC CTT CTC TAC AGT GAC CAG AAG	580	585	590	1824
Gly Asn Asp His Gly Ala Gln Asn Leu Leu Tyr Ser Asp Gln Lys				
AGG TGC TGA				1833
Arg Cys				

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 610 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Ser Val Trp Leu Val Phe Leu Val Cys Ala Gly Glu Lys Thr Thr
 -17 -15 -10 -5

Gly Phe Asn His Ser Ala Cys Ala Thr Lys Asn Ser Val Asp Ile Phe
 1 5 10 15

Ala Arg Gly Ala Glu Asn Phe Val Tyr Phe Val Thr Tyr Lys Ser Phe
 20 25 30

Arg Ser Lys Asn Ser Pro Met Gln Val Asn Cys His Gln His Lys Val
 35 40 45

Cys Ser Gln Thr Cys Ser Gly Ser Gln Lys Asp Leu Ser Asp Val Gln
 50 55 60

Trp Tyr Met Gln Pro Arg Ser Gly Ser Pro Leu Glu Glu Ile Ser Arg
 65 70 75

Asn Ser Pro His Met Gln Ser Glu Gly Met Leu His Ile Leu Ala Pro
 80 85 90 95

Gln Thr Asn Ser Ile Trp Ser Tyr Ile Cys Arg Pro Arg Ile Arg Ser
 100 105 110

Pro Gln Asp Met Ala Cys Cys Ile Lys Thr Val Leu Glu Val Lys Pro
 115 120 125

Gln Arg Asn Val Ser Cys Gly Asn Thr Ala Gln Asp Glu Gln Val Leu
 130 135 140

Leu Leu Gly Ser Thr Gly Ser Ile His Cys Pro Ser Leu Ser Cys Gln
 145 150 155

Ser Asp Val Gln Ser Pro Glu Met Thr Trp Tyr Lys Asp Gly Arg Leu
 160 165 170 175

Leu Pro Glu His Lys Lys Asn Pro Ile Glu Met Ala Asp Ile Tyr Val
 180 185 190

Phe Asn Gln Gly Leu Tyr Val Cys Asp Tyr Thr Gln Ser Asp Asn Val
 195 200 205

Ser Ser Trp Thr Val Arg Ala Val Val Lys Val Arg Thr Ile Gly Lys
 210 215 220

Asp Ile Asn Val Lys Pro Glu Ile Leu Asp Pro Ile Thr Asp Thr Leu
 225 230 235

Asp Val Glu Leu Gly Lys Pro Leu Thr Leu Pro Cys Arg Val Gln Phe
 240 245 250 255

Gly Phe Gln Arg Leu Ser Lys Pro Val Ile Lys Trp Tyr Val Lys Glu
 260 265 270

Ser Thr Gln Glu Trp Glu Met Ser Val Phe Glu Glu Lys Arg Ile Gln
 275 280 285

Ser Thr Phe Lys Asn Glu Val Ile Glu Arg Thr Ile Phe Leu Arg Glu
 290 295 300

Val Thr Gln Arg Asp Leu Ser Arg Lys Phe Val Cys Phe Ala Gln Asn
 305 310 315

Ser Ile Gly Asn Thr Thr Arg Thr Ile Arg Leu Arg Lys Lys Glu Glu
 320 325 330 335

Val Val Phe Val Tyr Ile Leu Leu Gly Thr Ala Leu Met Leu Val Gly
 340 345 350

Val Leu Val Ala Ala Ala Phe Leu Tyr Trp Tyr Trp Ile Glu Val Val
 355 360 365

Leu Leu Cys Arg Thr Tyr Lys Asn Lys Asp Glu Thr Leu Gly Asp Lys
 370 375 380

Lys Glu Phe Asp Ala Phe Val Ser Tyr Ser Asn Trp Ser Ser Pro Glu
 385 390 395

Thr Asp Ala Val Gly Ser Leu Ser Glu Glu His Leu Ala Leu Asn Leu
 400 405 410 415

Phe Pro Glu Val Leu Glu Asp Thr Tyr Gly Tyr Arg Leu Cys Leu Leu
 420 425 430

Asp Arg Asp Val Thr Pro Gly Gly Val Tyr Ala Asp Asp Ile Val Ser
 435 440 445

Ile Ile Lys Lys Ser Arg Arg Gly Ile Phe Ile Leu Ser Pro Ser Tyr
 450 455 460
 Leu Asn Gly Pro Arg Val Phe Glu Leu Gln Ala Ala Val Asn Leu Ala
 465 470 475
 Leu Val Asp Gln Thr Leu Lys Leu Ile Ile Lys Phe Cys Ser Phe
 480 485 490 495
 Gln Glu Pro Glu Ser Leu Pro Tyr Leu Val Lys Lys Ala Leu Arg Val
 500 505 510
 Leu Pro Thr Val Thr Trp Lys Gly Leu Lys Ser Val His Ala Ser Ser
 515 520 525
 Arg Phe Trp Thr Gln Ile Arg Tyr His Met Pro Val Lys Asn Ser Asn
 530 535 540
 Arg Phe Met Phe Asn Gly Leu Arg Ile Phe Leu Lys Gly Phe Ser Pro
 545 550 555
 Glu Lys Asp Leu Val Thr Gln Lys Pro Leu Glu Gly Met Pro Lys Ser
 560 565 570 575
 Gly Asn Asp His Gly Ala Gln Asn Leu Leu Leu Tyr Ser Asp Gln Lys
 580 585 590
 Arg Cys

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2259 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 22..1863

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TGACAGGGAGC AAAGGGGAAC C ATG CTC TGT TTG GGC TGG GTG TTT CTT TGG	51
Met Leu Cys Leu Gly Trp Val Phe Leu Trp	
1 5 10	
TTT GTT GCA GGA GAG AAG ACC ACA GGA TTT AAT CAT TCA GCT TGT GCC	99
Phe Val Ala Gly Glu Lys Thr Thr Gly Phe Asn His Ser Ala Cys Ala	
15 20 25	
ACC AAA AAA CTT CTG TGG ACA TAT TCT GCA AGG GGT GCA GAG AAT TTT	147
Thr Lys Lys Leu Leu Trp Thr Tyr Ser Ala Arg Gly Ala Glu Asn Phe	
30 35 40	
GTC CTA TTT TGT GAC TTA CAA GAG CTT CAG GAG CAA AAA TTC TCC CAT	195
Val Leu Phe Cys Asp Leu Gln Glu Leu Gln Glu Gln Lys Phe Ser His	
45 50 55	

GCA AGT CAA CTG TCA CCA ACA CAA AGT CCT GCT CAC AAA CCT TGC AGT Ala Ser Gln Leu Ser Pro Thr Gln Ser Pro Ala His Lys Pro Cys Ser 60 65 70	243
GGC AGT CAG AAG GAC CTA TCT GAT GTC CAG TGG TAC ATG CAA CCT CGG Gly Ser Gln Lys Asp Leu Ser Asp Val Gln Trp Tyr Met Gln Pro Arg 75 80 85 90	291
AGT GGA AGT CCA CTA GAG GAG ATC AGT AGA AAC TCT CCC CAT ATG CAG Ser Gly Ser Pro Leu Glu Ile Ser Arg Asn Ser Pro His Met Gln 95 100 105	339
AGT GAA GGC ATG CTG CAT ATA TTG GCC CCA CAG ACG AAC AGC ATT TGG Ser Glu Gly Met Leu His Ile Leu Ala Pro Gln Thr Asn Ser Ile Trp 110 115 120	387
TCA TAT ATT TGT AGA CCC AGA ATT AGG AGC CCC CAG GAT ATG GCC TGT Ser Tyr Ile Cys Arg Pro Arg Ile Arg Ser Pro Gln Asp Met Ala Cys 125 130 135	435
TGT ATC AAG ACA GTC TTA GAA GTT AAG CCT CAG AGA AAC GTG TCC TGT Cys Ile Lys Thr Val Leu Glu Val Lys Pro Gln Arg Asn Val Ser Cys 140 145 150	483
GGG AAC ACA GCA CAA GAT GAA CAA GTC CTA CTT CTT GGC AGT ACT GGC Gly Asn Thr Ala Gln Asp Glu Gln Val Leu Leu Gly Ser Thr Gly 155 160 165 170	531
TCC ATT CAT TGT CCC AGT CTC AGC TGC CAA AGT GAT GTA CAG AGT CCA Ser Ile His Cys Pro Ser Leu Ser Cys Gln Ser Asp Val Gln Ser Pro 175 180 185	579
GAG ATG ACC TGG TAC AAG GAT GGA AGA CTA CTT CCT GAG CAC AAG AAA Glu Met Thr Trp Tyr Lys Asp Gly Arg Leu Leu Pro Glu His Lys Lys 190 195 200	627
AAT CCA ATT GAG ATG GCA GAT ATT TAT GTT TTT AAT CAA GGC TTG TAT Asn Pro Ile Glu Met Ala Asp Ile Tyr Val Phe Asn Gln Gly Leu Tyr 205 210 215	675
GTA TGT GAT TAC ACA CAG TCA GAT AAT GTG AGT TCC TGG ACA GTC CGA Val Cys Asp Tyr Thr Gln Ser Asp Asn Val Ser Ser Trp Thr Val Arg 220 225 230	723
GCT GTG GTT AAA GTG AGA ACC ATT GGT AAG GAC ATC AAT GTG AAG CCG Ala Val Val Lys Val Arg Thr Ile Gly Lys Asp Ile Asn Val Lys Pro 235 240 245 250	771
GAA ATT CTG GAT CCC ATT ACA GAT ACA CTG GAC GTA GAG CTT GGA AAG Glu Ile Leu Asp Pro Ile Thr Asp Thr Leu Asp Val Glu Leu Gly Lys 255 260 265	819
CCT TTA ACT CTC CCC TGC AGA GTA CAG TTT GGC TTC CAA AGA CTT TCA Pro Leu Thr Leu Pro Cys Arg Val Gln Phe Gly Phe Gln Arg Leu Ser 270 275 280	867
AAG CCT GTG ATA AAG TGG TAT GTC AAA GAA TCT ACA CAG GAG TGG GAA Lys Pro Val Ile Lys Trp Tyr Val Lys Glu Ser Thr Gln Glu Trp Glu 285 290 295	915
ATG TCA GTA TTT GAG GAG AAA AGA ATT CAA TCC ACT TTC AAG AAT GAA Met Ser Val Phe Glu Glu Lys Arg Ile Gln Ser Thr Phe Lys Asn Glu 300 305 310	963

GTC ATT GAA CGT ACC ATC TTC TTG AGA GAA GTT ACC CAG AGA GAT CTC Val Ile Glu Arg Thr Ile Phe Leu Arg Glu Val Thr Gln Arg Asp Leu 315 320 325 330	1011
AGC AGA AAG TTT GTT TGC TTT GCC CAG AAC TCC ATT GGG AAC ACA ACA Ser Arg Lys Phe Val Cys Phe Ala Gln Asn Ser Ile Gly Asn Thr Thr 335 340 345	1059
CGG ACC ATA CGG CTG AGG AAG GAA GAG GTG GTG TTT GTA TAC ATC Arg Thr Ile Arg Leu Arg Lys Lys Glu Glu Val Val Phe Val Tyr Ile 350 355 360	1107
CTT CTC GGC ACG GCC TTG ATG CTG GTG GGC GTT CTG GTG GCA GCT GCT Leu Leu Gly Thr Ala Leu Met Leu Val Gly Val Leu Val Ala Ala Ala 365 370 375	1155
TTC CTC TAC TGG TAC TGG ATT GAA GTT GTC CTG CTC TGT CGA ACC TAC Phe Leu Tyr Trp Tyr Trp Ile Glu Val Val Leu Leu Cys Arg Thr Tyr 380 385 390	1203
AAG AAC AAA GAT GAG ACT CTG GGG GAT AAG AAG GAA TTC GAT GCA TTT Lys Asn Lys Asp Glu Thr Leu Gly Asp Lys Lys Glu Phe Asp Ala Phe 395 400 405 410	1251
GTA TCC TAC TCG AAT TGG AGC TCT CCT GAG ACT GAC GCC GTG GGA TCT Val Ser Tyr Ser Asn Trp Ser Ser Pro Glu Thr Asp Ala Val Gly Ser 415 420 425	1299
CTG AGT GAG GAA CAC CTG GCT CTG AAT CTT TTC CCG GAA GTG CTA GAA Leu Ser Glu Glu His Leu Ala Leu Asn Leu Phe Pro Glu Val Leu Glu 430 435 440	1347
GAC ACC TAT GGG TAC AGA TTG TGT TTG CTT GAC CGA GAT GTG ACC CCA Asp Thr Tyr Gly Tyr Arg Leu Cys Leu Leu Asp Arg Asp Val Thr Pro 445 450 455	1395
GGA GGA GTG TAT GCA GAT GAC ATT GTG AGC ATC ATT AAG AAA AGC CGA Gly Gly Val Tyr Ala Asp Asp Ile Val Ser Ile Ile Lys Lys Ser Arg 460 465 470	1443
AGA GGA ATA TTT ATC CTG AGT CCC AGC TAC CTC AAT GGA CCC CGT GTC Arg Gly Ile Phe Ile Leu Ser Pro Ser Tyr Leu Asn Gly Pro Arg Val 475 480 485 490	1491
TTT GAG CTA CAA GCA GCA GTG AAT CTT GCC TTG GTT GAT CAG ACA CTG Phe Glu Leu Gln Ala Ala Val Asn Leu Ala Leu Val Asp Gln Thr Leu 495 500 505	1539
AAG TTG ATT TTA ATT AAG TTC TGT TCC TTC CAA GAG CCA GAA TCT CTT Lys Leu Ile Leu Ile Lys Phe Cys Ser Phe Gln Glu Pro Glu Ser Leu 510 515 520	1587
CCT TAC CTT GTC AAA AAG GCT CTG CGG GTT CTC CCC ACA GTC ACA TGG Pro Tyr Leu Val Lys Lys Ala Leu Arg Val Leu Pro Thr Val Thr Trp 525 530 535	1635
AAA GGC TTG AAG TCG GTC CAC GCC AGT TCC AGG TTC TGG ACC CAA ATT Lys Gly Leu Lys Ser Val His Ala Ser Ser Arg Phe Trp Thr Gln Ile 540 545 550	1683
CGT TAC CAC ATG CCT GTG AAG AAC TCC AAC AGG TTT ATG TTC AAC GGG Arg Tyr His Met Pro Val Lys Asn Ser Asn Arg Phe Met Phe Asn Gly 555 560 565 570	1731

CTC AGA ATT TTC CTG AAG GGC TTT TCC CCT GAA AAG GAC CTA GTG ACA Leu Arg Ile Phe Leu Lys Gly Phe Ser Pro Glu Lys Asp Leu Val Thr 575 580 585	1779
CAG AAA CCC CTG GAA GGA ATG CCC AAG TCT GGG AAT GAC CAC GGA GCT Gln Lys Pro Leu Glu Gly Met Pro Lys Ser Gly Asn Asp His Gly Ala 590 595 600	1827
CAG AAC CTC CTT CTC TAC AGT GAC CAG AAG AGG TGC TGATGGGTAG Gln Asn Leu Leu Tyr Ser Asp Gln Lys Arg Cys 605 610	1873
AACTTGCTGT GTGGATCAGG CTGATAGAAA TTGAGCCTTT CTGCTCTCAG TGCCAAGCAA GCCTGACAGG CAGTGGATG AAGCGGCATC TGTGGTTTA GGGTCTGGGT TCCTGGAACA GACACAGAGC AATACTCCAG ACCTCTGCCG TGTGCTTAGC ACACATTCC CTGAGAGTTC CCAAGTAGCC TGAACAGAAT CAACAGAAAT AGCTCCATGG GCTGTCCAAC ATTCAATGCAC GCATGCCTGT TTTGCACTAT ATATATGAAT TTATCATAAG TTTGTGTGTG TATATGCATT CAGATAAATA GGATTTATT TTGTTCGATA CGAGTGATTG AAACTCCATC TAAAGCCCTT CTGTAAAGAA AAAAAAAA AAAAAA	1933 1993 2053 2113 2173 2233 2259

(2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 614 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Leu Cys Leu Gly Trp Val Phe Leu Trp Phe Val Ala Gly Glu Lys 1 5 10 15
Thr Thr Gly Phe Asn His Ser Ala Cys Ala Thr Lys Lys Leu Leu Trp 20 25 30
Thr Tyr Ser Ala Arg Gly Ala Glu Asn Phe Val Leu Phe Cys Asp Leu 35 40 45
Gln Glu Leu Gln Glu Gln Lys Phe Ser His Ala Ser Gln Leu Ser Pro 50 55 60
Thr Gln Ser Pro Ala His Lys Pro Cys Ser Gly Ser Gln Lys Asp Leu 65 70 75 80
Ser Asp Val Gln Trp Tyr Met Gln Pro Arg Ser Gly Ser Pro Leu Glu 85 90 95
Glu Ile Ser Arg Asn Ser Pro His Met Gln Ser Glu Gly Met Leu His 100 105 110
Ile Leu Ala Pro Gln Thr Asn Ser Ile Trp Ser Tyr Ile Cys Arg Pro 115 120 125
Arg Ile Arg Ser Pro Gln Asp Met Ala Cys Cys Ile Lys Thr Val Leu 130 135 140

Glu Val Lys Pro Gln Arg Asn Val Ser Cys Gly Asn Thr Ala Gln Asp
 145 150 155 160
 Glu Gln Val Leu Leu Leu Gly Ser Thr Gly Ser Ile His Cys Pro Ser
 165 170 175
 Leu Ser Cys Gln Ser Asp Val Gln Ser Pro Glu Met Thr Trp Tyr Lys
 180 185 190
 Asp Gly Arg Leu Leu Pro Glu His Lys Lys Asn Pro Ile Glu Met Ala
 195 200 205
 Asp Ile Tyr Val Phe Asn Gln Gly Leu Tyr Val Cys Asp Tyr Thr Gln
 210 215 220
 Ser Asp Asn Val Ser Ser Trp Thr Val Arg Ala Val Val Lys Val Arg
 225 230 235 240
 Thr Ile Gly Lys Asp Ile Asn Val Lys Pro Glu Ile Leu Asp Pro Ile
 245 250 255
 Thr Asp Thr Leu Asp Val Glu Leu Gly Lys Pro Leu Thr Leu Pro Cys
 260 265 270
 Arg Val Gln Phe Gly Phe Gln Arg Leu Ser Lys Pro Val Ile Lys Trp
 275 280 285
 Tyr Val Lys Glu Ser Thr Gln Glu Trp Glu Met Ser Val Phe Glu Glu
 290 295 300
 Lys Arg Ile Gln Ser Thr Phe Lys Asn Glu Val Ile Glu Arg Thr Ile
 305 310 315 320
 Phe Leu Arg Glu Val Thr Gln Arg Asp Leu Ser Arg Lys Phe Val Cys
 325 330 335
 Phe Ala Gln Asn Ser Ile Gly Asn Thr Thr Arg Thr Ile Arg Leu Arg
 340 345 350
 Lys Lys Glu Glu Val Val Phe Val Tyr Ile Leu Leu Gly Thr Ala Leu
 355 360 365
 Met Leu Val Gly Val Leu Val Ala Ala Ala Phe Leu Tyr Trp Tyr Trp
 370 375 380
 Ile Glu Val Val Leu Leu Cys Arg Thr Tyr Lys Asn Lys Asp Glu Thr
 385 390 395 400
 Leu Gly Asp Lys Lys Glu Phe Asp Ala Phe Val Ser Tyr Ser Asn Trp
 405 410 415
 Ser Ser Pro Glu Thr Asp Ala Val Gly Ser Leu Ser Glu Glu His Leu
 420 425 430
 Ala Leu Asn Leu Phe Pro Glu Val Leu Glu Asp Thr Tyr Gly Tyr Arg
 435 440 445
 Leu Cys Leu Leu Asp Arg Asp Val Thr Pro Gly Gly Val Tyr Ala Asp
 450 455 460
 Asp Ile Val Ser Ile Ile Lys Lys Ser Arg Arg Gly Ile Phe Ile Leu
 465 470 475 480

Ser Pro Ser Tyr Leu Asn Gly Pro Arg Val Phe Glu Leu Gln Ala Ala.
 485 490 495

Val Asn Leu Ala Leu Val Asp Gln Thr Leu Lys Leu Ile Leu Ile Lys
 500 505 510

Phe Cys Ser Phe Gln Glu Pro Glu Ser Leu Pro Tyr Leu Val Lys Lys
 515 520 525

Ala Leu Arg Val Leu Pro Thr Val Thr Trp Lys Gly Leu Lys Ser Val
 530 535 540

His Ala Ser Ser Arg Phe Trp Thr Gln Ile Arg Tyr His Met Pro Val
 545 550 555 560

Lys Asn Ser Asn Arg Phe Met Phe Asn Gly Leu Arg Ile Phe Leu Lys
 565 570 575

Gly Phe Ser Pro Glu Lys Asp Leu Val Thr Gln Lys Pro Leu Glu Gly
 580 585 590

Met Pro Lys Ser Gly Asn Asp His Gly Ala Gln Asn Leu Leu Tyr
 595 600 605

Ser Asp Gln Lys Arg Cys
 610

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 516 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 2..514

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 374
- (D) OTHER INFORMATION: /note= "nucleotides 374, 383, 396, 403, 433, 458, 459, 483, and 515 are indicated as C; each may be A, C, G, or T"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

C TGT GAA TTA AAA TAT GGA GGC TTT GTT GTG AGA AGA ACT ACT GAA	46
Cys Glu Leu Lys Tyr Gly Gly Phe Val Val Arg Arg Thr Thr Glu	
1 5 10 15	
TTA ACT GTT ACA GCC CCT CTG ACT GAT AAG CCA CCC AAG CTT TTG TAT	94
Leu Thr Val Thr Ala Pro Leu Thr Asp Lys Pro Pro Lys Leu Leu Tyr	
20 25 30	
CCT ATG GAA AGT AAA CTG ACA ATT CAG GAG ACC CAG CTG GGT GAC TCT	142
Pro Met Glu Ser Lys Leu Thr Ile Gln Glu Thr Gln Leu Gly Asp Ser	
35 40 45	

GCT AAT CTA ACC TGC AGA GCT TTC TTT GGG TAC AGC GGA GAT GTC AGT Ala Asn Leu Thr Cys Arg Ala Phe Phe Gly Tyr Ser Gly Asp Val Ser 50 55 60	190
CCT TTA ATT TAC TGG ATG AAA GGA GAA AAA TTT ATT GAA GAT CTG GAT Pro Leu Ile Tyr Trp Met Lys Gly Glu Lys Phe Ile Glu Asp Leu Asp 65 70 75	238
GAA AAT CGA GTT TGG GAA AGT GAC ATT AGA ATT CTT AAG GAG CAT CTT Glu Asn Arg Val Trp Glu Ser Asp Ile Arg Ile Leu Lys Glu His Leu 80 85 90 95	286
GGG GAA CAG GAA GTT TCC ATC TCA TTA ATT GTG GAC TCT GTG GAA GAA Gly Glu Gln Glu Val Ser Ile Ser Leu Ile Val Asp Ser Val Glu Glu 100 105 110	334
GGT GAC TTG GGA AAT TAC TCC TGT TAT GTT GAA AAA TGG CAA TGG ACG Gly Asp Leu Gly Asn Tyr Ser Cys Tyr Val Glu Lys Trp Gln Trp Thr 115 120 125	382
CCG ACA CGC CAG CCG TCC CCC TTC ATA AAC GAG AGC CTA ATG TAC ACA Pro Thr Arg Gln Pro Ser Pro Phe Ile Asn Glu Ser Leu Met Tyr Thr 130 135 140	430
GTC GGA ACT TGC CTG GAG GCC CTT GGG CCA AAA CCT TGG TGG TTG AAT Val Gly Thr Cys Leu Glu Ala Leu Gly Pro Lys Pro Trp Trp Leu Asn 145 150 155	478
GTT TCG GGA CCA CCT TCA AAG TGT ACC AAG GTT GGA CC Val Ser Gly Pro Pro Ser Lys Cys Thr Lys Val Gly 160 165 170	516

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 171 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Cys Glu Leu Lys Tyr Gly Gly Phe Val Val Arg Arg Thr Thr Glu Leu 1 5 10 15
Thr Val Thr Ala Pro Leu Thr Asp Lys Pro Pro Lys Leu Leu Tyr Pro 20 25 30
Met Glu Ser Lys Leu Thr Ile Gln Glu Thr Gln Leu Gly Asp Ser Ala 35 40 45
Asn Leu Thr Cys Arg Ala Phe Phe Gly Tyr Ser Gly Asp Val Ser Pro 50 55 60
Leu Ile Tyr Trp Met Lys Gly Glu Lys Phe Ile Glu Asp Leu Asp Glu 65 70 75 80
Asn Arg Val Trp Glu Ser Asp Ile Arg Ile Leu Lys Glu His Leu Gly 85 90 95
Glu Gln Glu Val Ser Ile Ser Leu Ile Val Asp Ser Val Glu Glu Gly 100 105 110

Asp Leu Gly Asn Tyr Ser Cys Tyr Val Glu Lys Trp Gln Trp Thr Pro
 115 120 125

Thr Arg Gln Pro Ser Pro Phe Ile Asn Glu Ser Leu Met Tyr Thr Val
 130 135 140

Gly Thr Cys Leu Glu Ala Leu Gly Pro Lys Pro Trp Trp Leu Asn Val
 145 150 155 160

Ser Gly Pro Pro Ser Lys Cys Thr Lys Val Gly
 165 170

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1991 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 1..1458

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GAA TTC GGC ACG AGC TGT GAA TTA AAA TAT GGA GGC TTT GTT GTG AGA	48
Glu Phe Gly Thr Ser Cys Glu Leu Lys Tyr Gly Phe Val Val Arg	
1 5 10 15	
AGA ACT ACT GAA TTA ACT GTT ACA GCC CCT CTG ACT GAT AAG CCA CCC	96
Arg Thr Thr Glu Leu Thr Val Thr Ala Pro Leu Thr Asp Lys Pro Pro	
20 25 30	
AAG CTT TTG TAT CCT ATG GAA AGT AAA CTG ACA ATT CAG GAG ACC CAG	144
Lys Leu Leu Tyr Pro Met Glu Ser Lys Leu Thr Ile Gln Glu Thr Gln	
35 40 45	
CTG GGT GAC TCT GCT AAT CTA ACC TGC AGA GCT TTC TTT GGG TAC AGC	192
Leu Gly Asp Ser Ala Asn Leu Thr Cys Arg Ala Phe Phe Gly Tyr Ser	
50 55 60	
GGA GAT GTC AGT CCT TTA ATT TAC TGG ATG AAA GGA GAA AAA TTT ATT	240
Gly Asp Val Ser Pro Leu Ile Tyr Trp Met Lys Gly Glu Lys Phe Ile	
65 70 75 80	
GAA GAT CTG GAT GAA AAT CGA GTT TGG GAA AGT GAC ATT AGA ATT CTT	288
Glu Asp Leu Asp Glu Asn Arg Val Trp Glu Ser Asp Ile Arg Ile Leu	
85 90 95	
AAG GAG CAT CTT GGG GAA CAG GAA GTT TCC ATC TCA TTA ATT GTG GAC	336
Lys Glu His Leu Gly Glu Gln Glu Val Ser Ile Ser Leu Ile Val Asp	
100 105 110	
TCT GTG GAA GAA GGT GAC TTG GGA AAT TAC TCC TGT TAT GTT GAA AAT	384
Ser Val Glu Glu Gly Asp Leu Gly Asn Tyr Ser Cys Tyr Val Glu Asn	
115 120 125	

GGA AAT GGA CGT CGA CAC GCC AGC GTT CTC CTT CAT AAA CGA GAG CTA	432
Gly Asn Gly Arg Arg His Ala Ser Val Leu Leu His Lys Arg Glu Leu	
130 135 140	
ATG TAC ACA GTG GAA CTT GCT GGA GGC CTT GGT GCT ATA CTC TTG CTG	480
Met Tyr Thr Val Glu Leu Ala Gly Gly Leu Gly Ala Ile Leu Leu Leu	
145 150 155 160	
CTT GTA TGT TTG GTG ACC ATC TAC AAG TGT TAC AAG ATA GAA ATC ATG	528
Leu Val Cys Leu Val Thr Ile Tyr Lys Cys Tyr Lys Ile Glu Ile Met	
165 170 175	
CTC TTC TAC AGG AAT CAT TTT GGA GCT GAA GAG CTC GAT GGA GAC AAT	576
Leu Phe Tyr Arg Asn His Phe Gly Ala Glu Glu Leu Asp Gly Asp Asn	
180 185 190	
AAA GAT TAT GAT GCA TAC TTA TCA TAC ACC AAA GTG GAT CCT GAC CAG	624
Lys Asp Tyr Asp Ala Tyr Leu Ser Tyr Thr Lys Val Asp Pro Asp Gln	
195 200 205	
TGG AAT CAA GAG ACT GGG GAA GAA GAA CGT TTT GCC CTT GAA ATC CTA	672
Trp Asn Gln Glu Thr Gly Glu Glu Arg Phe Ala Leu Glu Ile Leu	
210 215 220	
CCT GAT ATG CTT GAA AAG CAT TAT GGA TAT AAG TTG TTT ATA CCA GAT	720
Pro Asp Met Leu Glu Lys His Tyr Gly Tyr Lys Leu Phe Ile Pro Asp	
225 230 235 240	
AGA GAT TTA ATC CCA ACT GGA ACA TAC ATT GAA GAT GTG GCA AGA TGT	768
Arg Asp Leu Ile Pro Thr Gly Thr Tyr Ile Glu Asp Val Ala Arg Cys	
245 250 255	
GTA GAT CAA AGC AAG CGG CTG ATT ATT GTC ATG ACC CCA AAT TAC GTA	816
Val Asp Gln Ser Lys Arg Leu Ile Ile Val Met Thr Pro Asn Tyr Val	
260 265 270	
GTT AGA AGG GGC TGG AGC ATC TTT GAG CTG GAA ACC AGA CTT CGA AAT	864
Val Arg Arg Gly Trp Ser Ile Phe Glu Leu Glu Thr Arg Leu Arg Asn	
275 280 285	
ATG CTT GTG ACT GGA GAA ATT AAA GTG ATT CTA ATT GAA TGC AGT GAA	912
Met Leu Val Thr Gly Glu Ile Lys Val Ile Leu Ile Glu Cys Ser Glu	
290 295 300	
CTG AGA GGA ATT ATG AAC TAC CAG GAG GTG GAG GCC CTG AAG CAC ACC	960
Leu Arg Gly Ile Met Asn Tyr Gln Glu Val Ala Leu Lys His Thr	
305 310 315 320	
ATC AAG CTC CTG ACG GTC ATT AAA TGG CAT GGA CCA AAA TGC AAC AAG	1008
Ile Lys Leu Leu Thr Val Ile Lys Trp His Gly Pro Lys Cys Asn Lys	
325 330 335	
TTG AAC TCC AAG TTC TGG AAA CGT TTA CAG TAT GAA ATG CCT TTT AAG	1056
Leu Asn Ser Lys Phe Trp Lys Arg Leu Gln Tyr Glu Met Pro Phe Lys	
340 345 350	
AGG ATA GAA CCC ATT ACA CAT GAG CAG GCT TTA GAT GTC AGT GAG CAA	1104
Arg Ile Glu Pro Ile Thr His Glu Gln Ala Leu Asp Val Ser Glu Gln	
355 360 365	
GGG CCT TTT GGG GAG CTG CAG ACT GTC TCG GCC ATT TCC ATG GCC GCG	1152
Gly Pro Phe Gly Glu Leu Gln Thr Val Ser Ala Ile Ser Met Ala Ala	
370 375 380	

GCC ACC TCC ACA GCT CTA GCC ACT GCC CAT CCA GAT CTC CGT TCT ACC Ala Thr Ser Thr Ala Leu Ala Thr Ala His Pro Asp Leu Arg Ser Thr 385 390 395 400	1200
TTT CAC AAC ACG TAC CAT TCA CAA ATG CGT CAG AAA CAC TAC TAC CGA Phe His Asn Thr Tyr His Ser Gln Met Arg Gln Lys His Tyr Tyr Arg 405 410 415	1248
AGC TAT GAG TAC GAC GTA CCT CCT ACC GGC ACC CTG CCT CTT ACC TCC Ser Tyr Glu Tyr Asp Val Pro Pro Thr Gly Thr Leu Pro Leu Thr Ser 420 425 430	1296
ATA GGC AAT CAG CAT ACC TAC TGT AAC ATC CCT ATG ACA CTC ATC AAC Ile Gly Asn Gln His Thr Tyr Cys Asn Ile Pro Met Thr Leu Ile Asn 435 440 445	1344
GGG CAG CGG CCA CAG ACA AAA TCG AGC AGG GAG CAG AAT CCA GAT GAG Gly Gln Arg Pro Gln Thr Lys Ser Ser Arg Glu Gln Asn Pro Asp Glu 450 455 460	1392
GCC CAC ACA AAC AGT GCC ATC CTG CCG CTG TTG CCA AGG GAG ACC AGT Ala His Thr Asn Ser Ala Ile Leu Pro Leu Leu Pro Arg Glu Thr Ser 465 470 475 480	1440
ATA TCC AGT GTG ATA TGG TGACAGAAAA GCAAGGGACA TCCCGTCCCT Ile Ser Ser Val Ile Trp 485	1488
GGGAGGTTGA GTGGAATCTG CAGTCCAGTG CCTGGAACTA AATCCTCGAC TGCTGCTGTT AAAAAACATG CATTAGAACAC TTTAGAACAC GAGGAAAAAC AGGGTCTTGT ACATATGTTT TTTGGAAATTCTTTGTAGCA TCAGTGTCCCT CCTGTTTAC CATGTCTTTT ACCATTACAT TTTTTGACTT TGTTTTATAT GTCGTTGGAA TTTGTAAATT TACATTTTTT TTAAAGAAGA GACTGATGTG TAGATAGAAA ACCCTTTTT TGCTTCATTA GTTGTAGTTT AGAATGGGTT TTTATTTTAT TTCCCTTTTT AAAATTTTAC TTTGCTTTA ACATTTCCCTT GGGGTGCTTG AACAAATCTA TCCGATGGGA CAAGGAGCAC CGGATTCTTT CTCGGGTTCT GCCTAGCATC AACTGGGCCA CGTCGGCCTT CAGAGAACAG TGCAACAAAT GCCAGCATTG CCATTGGGG GGAAAAAAAAA AAAAAAAAAA AAA	1548 1608 1668 1728 1788 1848 1908 1968 1991

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 486 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Glu Phe Gly Thr Ser Cys Glu Leu Lys Tyr Gly Gly Phe Val Val Arg
1 5 10 15

Arg Thr Thr Glu Leu Thr Val Thr Ala Pro Leu Thr Asp Lys Pro Pro
20 25 30

Lys Leu Leu Tyr Pro Met Glu Ser Lys Leu Thr Ile Gln Glu Thr Gln
 35 40 45

Leu Gly Asp Ser Ala Asn Leu Thr Cys Arg Ala Phe Phe Gly Tyr Ser
 50 55 60

Gly Asp Val Ser Pro Leu Ile Tyr Trp Met Lys Gly Glu Lys Phe Ile
 65 70 75 80

Glu Asp Leu Asp Glu Asn Arg Val Trp Glu Ser Asp Ile Arg Ile Leu
 85 90 95

Lys Glu His Leu Gly Glu Gln Glu Val Ser Ile Ser Leu Ile Val Asp
 100 105 110

Ser Val Glu Glu Gly Asp Leu Gly Asn Tyr Ser Cys Tyr Val Glu Asn
 115 120 125

Gly Asn Gly Arg Arg His Ala Ser Val Leu Leu His Lys Arg Glu Leu
 130 135 140

Met Tyr Thr Val Glu Leu Ala Gly Gly Leu Gly Ala Ile Leu Leu Leu
 145 150 155 160

Leu Val Cys Leu Val Thr Ile Tyr Lys Cys Tyr Lys Ile Glu Ile Met
 165 170 175

Leu Phe Tyr Arg Asn His Phe Gly Ala Glu Glu Leu Asp Gly Asp Asn
 180 185 190

Lys Asp Tyr Asp Ala Tyr Leu Ser Tyr Thr Lys Val Asp Pro Asp Gln
 195 200 205

Trp Asn Gln Glu Thr Gly Glu Glu Arg Phe Ala Leu Glu Ile Leu
 210 215 220

Pro Asp Met Leu Glu Lys His Tyr Gly Tyr Lys Leu Phe Ile Pro Asp
 225 230 235 240

Arg Asp Leu Ile Pro Thr Gly Thr Tyr Ile Glu Asp Val Ala Arg Cys
 245 250 255

Val Asp Gln Ser Lys Arg Leu Ile Ile Val Met Thr Pro Asn Tyr Val
 260 265 270

Val Arg Arg Gly Trp Ser Ile Phe Glu Leu Glu Thr Arg Leu Arg Asn
 275 280 285

Met Leu Val Thr Gly Glu Ile Lys Val Ile Leu Ile Glu Cys Ser Glu
 290 295 300

Leu Arg Gly Ile Met Asn Tyr Gln Glu Val Glu Ala Leu Lys His Thr
 305 310 315 320

Ile Lys Leu Leu Thr Val Ile Lys Trp His Gly Pro Lys Cys Asn Lys
 325 330 335

Leu Asn Ser Lys Phe Trp Lys Arg Leu Gln Tyr Glu Met Pro Phe Lys
 340 345 350

Arg Ile Glu Pro Ile Thr His Glu Gln Ala Leu Asp Val Ser Glu Gln
 355 360 365

Gly Pro Phe Gly Glu Leu Gln Thr Val Ser Ala Ile Ser Met Ala Ala
 370 375 380
 Ala Thr Ser Thr Ala Leu Ala Thr Ala His Pro Asp Leu Arg Ser Thr
 385 390 395 400
 Phe His Asn Thr Tyr His Ser Gln Met Arg Gln Lys His Tyr Tyr Arg
 405 410 415
 Ser Tyr Glu Tyr Asp Val Pro Pro Thr Gly Thr Leu Pro Leu Thr Ser
 420 425 430
 Ile Gly Asn Gln His Thr Tyr Cys Asn Ile Pro Met Thr Leu Ile Asn
 435 440 445
 Gly Gln Arg Pro Gln Thr Lys Ser Ser Arg Glu Gln Asn Pro Asp Glu
 450 455 460
 Ala His Thr Asn Ser Ala Ile Leu Pro Leu Leu Pro Arg Glu Thr Ser
 465 470 475 480
 Ile Ser Ser Val Ile Trp
 485

(2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 570 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Met Gly Leu Leu Trp Tyr Leu Met Ser Leu Ser Phe Tyr Gly Ile Leu
 1 5 10 15
 Gln Ser His Ala Ser Glu Arg Cys Asp Asp Trp Gly Leu Asp Thr Met
 20 25 30
 Arg Gln Ile Gln Val Phe Glu Asp Glu Pro Ala Arg Ile Lys Cys Pro
 35 40 45
 Leu Phe Glu His Phe Leu Lys Tyr Asn Tyr Ser Thr Ala His Ser Ser
 50 55 60
 Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
 65 70 75 80
 Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
 85 90 95
 Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
 100 105 110
 Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
 115 120 125

Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Ala Met Arg Phe
 130 135 140
 Pro Val His Lys Met Tyr Ile Glu His Gly Ile His Lys Ile Thr Cys
 145 150 155 160
 Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Ser Val Thr
 165 170 175
 Trp Tyr Lys Gly Cys Thr Glu Ile Val Asp Phe His Asn Val Leu Pro
 180 185 190
 Glu Gly Met Asn Leu Ser Phe Phe Ile Pro Leu Val Ser Asn Asn Gly
 195 200 205
 Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Leu Phe His
 210 215 220
 Leu Thr Arg Thr Val Thr Val Lys Val Val Gly Ser Pro Lys Asp Ala
 225 230 235 240
 Leu Pro Pro Gln Ile Tyr Ser Pro Asn Asp Arg Val Val Tyr Glu Lys
 245 250 255
 Glu Pro Gly Glu Glu Leu Val Ile Pro Cys Lys Val Tyr Phe Ser Phe
 260 265 270
 Ile Met Asp Ser His Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
 275 280 285
 Pro Asp Asp Val Thr Val Asp Ile Thr Ile Asn Glu Ser Val Ser Tyr
 290 295 300
 Ser Ser Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
 305 310 315 320
 Val Thr Pro Glu Asp Leu Arg Arg Asn Tyr Val Cys His Ala Arg Asn
 325 330 335
 Thr Lys Gly Glu Ala Glu Gln Ala Ala Lys Val Lys Gln Lys Val Ile
 340 345 350
 Pro Pro Arg Tyr Thr Val Glu Leu Ala Cys Gly Phe Gly Ala Thr Val
 355 360 365
 Phe Leu Val Val Val Leu Ile Val Val Tyr His Val Tyr Trp Leu Glu
 370 375 380
 Met Val Leu Phe Tyr Arg Ala His Phe Gly Thr Asp Glu Thr Ile Leu
 385 390 395 400
 Asp Gly Lys Glu Tyr Asp Ile Tyr Val Ser Tyr Ala Arg Asn Val Glu
 405 410 415
 Glu Glu Glu Phe Val Leu Leu Thr Leu Arg Gly Val Leu Glu Asn Glu
 420 425 430
 Phe Gly Tyr Lys Leu Cys Ile Phe Asp Arg Asp Ser Leu Pro Gly Gly
 435 440 445
 Ile Val Thr Asp Glu Thr Leu Ser Phe Ile Gln Lys Ser Arg Arg Leu
 450 455 460

Leu Val Val Leu Ser Pro Asn Tyr Val Leu Gln Gly Thr Gln-Ala Leu
 465 470 475 480

Leu Glu Leu Lys Ala Gly Leu Glu Asn Met Ala Ser Arg Gly Asn Ile
 485 490 495

Asn Val Ile Leu Val Gln Tyr Lys Ala Val Lys Asp Met Lys Val Lys
 500 505 510

Glu Leu Lys Arg Ala Lys Thr Val Leu Thr Val Ile Lys Trp Lys Gly
 515 520 525

Glu Lys Ser Lys Tyr Pro Gln Gly Arg Phe Trp Lys Gln Leu Gln Val
 530 535 540

Ala Met Pro Val Lys Lys Ser Pro Arg Trp Ser Ser Asn Asp Lys Gln
 545 550 555 560

Gly Leu Ser Tyr Ser Ser Leu Lys Asn Val
 565 570

(2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 562 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met Trp Ser Leu Leu Leu Cys Gly Leu Ser Ile Ala Leu Pro Leu Ser
 1 5 10 15

Val Thr Ala Asp Gly Cys Lys Asp Ile Phe Met Lys Asn Glu Ile Leu
 20 25 30

Ser Ala Ser Gln Pro Phe Ala Phe Asn Cys Thr Phe Pro Pro Ile Thr
 35 40 45

Ser Gly Glu Val Ser Val Thr Trp Tyr Lys Asn Ser Ser Lys Ile Pro
 50 55 60

Val Ser Lys Ile Ile Gln Ser Arg Ile His Gln Asp Glu Thr Trp Ile
 65 70 75 80

Leu Phe Leu Pro Met Glu Trp Gly Asp Ser Gly Val Tyr Gln Cys Val
 85 90 95

Ile Lys Gly Arg Asp Ser Cys His Arg Ile His Val Asn Leu Thr Val
 100 105 110

Phe Glu Lys His Trp Cys Asp Thr Ser Ile Gly Gly Leu Pro Asn Leu
 115 120 125

Ser Asp Glu Tyr Lys Gln Ile Leu His Leu Gly Lys Asp Asp Ser Leu
 130 135 140

Thr Cys His Leu His Phe Pro Lys Ser Cys Val Leu Gly Pro Ile Lys
 145 150 155 160
 Trp Tyr Lys Asp Cys Asn Glu Ile Lys Gly Glu Arg Phe Thr Val Leu
 165 170 175
 Glu Thr Arg Leu Leu Val Ser Asn Val Ser Ala Glu Asp Arg Gly Asn
 180 185 190
 Tyr Ala Cys Gln Ala Ile Leu Thr His Ser Gly Lys Gln Tyr Glu Val
 195 200 205
 Leu Asn Gly Ile Thr Val Ser Ile Thr Glu Arg Ala Gly Tyr Gly Gly
 210 215 220
 Ser Val Pro Lys Ile Ile Tyr Pro Lys Asn His Ser Ile Glu Val Gln
 225 230 235 240
 Leu Gly Thr Thr Leu Ile Val Asp Cys Asn Val Thr Asp Thr Lys Asp
 245 250 255
 Asn Thr Asn Leu Arg Cys Trp Arg Val Asn Asn Thr Leu Val Asp Asp
 260 265 270
 Tyr Tyr Asp Glu Ser Lys Arg Ile Arg Glu Gly Val Glu Thr His Val
 275 280 285
 Ser Phe Arg Glu His Asn Leu Tyr Thr Val Asn Ile Thr Phe Leu Glu
 290 295 300
 Val Lys Met Glu Asp Tyr Gly Leu Pro Phe Met Cys His Ala Gly Val
 305 310 315 320
 Ser Thr Ala Tyr Ile Ile Leu Gln Leu Pro Ala Pro Asp Phe Arg Ala
 325 330 335
 Tyr Leu Ile Gly Gly Leu Ile Ala Leu Val Ala Val Ala Val Ser Val
 340 345 350
 Val Tyr Ile Tyr Asn Ile Phe Lys Ile Asp Ile Val Leu Trp Tyr Arg
 355 360 365
 Ser Ala Phe His Ser Thr Glu Thr Ile Val Asp Gly Lys Leu Tyr Asp
 370 375 380
 Ala Tyr Val Leu Tyr Pro Lys Pro His Lys Glu Ser Gln Arg His Ala
 385 390 395 400
 Val Asp Ala Leu Val Leu Asn Ile Leu Pro Glu Val Leu Glu Arg Gln
 405 410 415
 Cys Gly Tyr Lys Leu Phe Ile Phe Gly Arg Asp Glu Phe Pro Gly Gln
 420 425 430
 Ala Val Ala Asn Val Ile Asp Glu Asn Val Lys Leu Cys Arg Arg Leu
 435 440 445
 Ile Val Ile Val Val Pro Glu Ser Leu Gly Phe Gly Leu Leu Lys Asn
 450 455 460
 Leu Ser Glu Glu Gln Ile Ala Val Tyr Ser Ala Leu Ile Gln Asp Gly
 465 470 475 480

Met Lys Val Ile Leu Ile Glu Leu Glu Lys Ile Glu Asp Tyr-Thr Val
 485 490 495

Met Pro Glu Ser Ile Gln Tyr Ile Lys Gln Lys His Gly Ala Ile Arg
 500 505 510

Trp His Gly Asp Phe Thr Glu Gln Ser Gln Cys Met Lys Thr Lys Phe
 515 520 525

Trp Lys Thr Val Arg Tyr His Met Pro Pro Arg Arg Cys Arg Pro Phe
 530 535 540

Leu Arg Ser Thr Cys Arg Ser Thr His Leu Cys Thr Ala Pro Gln Ala
 545 550 555 560

Gln Asn

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 561 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Met Gly Met Pro Pro Leu Leu Phe Cys Trp Val Ser Phe Val Leu Pro
 1 5 10 15

Leu Phe Val Ala Ala Gly Asn Cys Thr Asp Val Tyr Met His His Glu
 20 25 30

Met Ile Ser Glu Gly Gln Pro Phe Pro Phe Asn Cys Thr Tyr Pro Pro
 35 40 45

Val Thr Asn Gly Ala Val Asn Leu Thr Trp His Arg Thr Pro Ser Lys
 50 55 60

Ser Pro Ile Ser Ile Asn Arg His Val Arg Ile His Gln Asp Gln Ser
 65 70 75 80

Trp Ile Leu Phe Leu Pro Leu Ala Leu Glu Asp Ser Gly Ile Tyr Gln
 85 90 95

Cys Val Ile Lys Asp Ala His Ser Cys Tyr Arg Ile Ala Ile Asn Leu
 100 105 110

Thr Val Phe Arg Lys His Trp Cys Asp Ser Ser Asn Glu Glu Ser Ser
 115 120 125

Ile Asn Ser Ser Asp Glu Tyr Gln Gln Trp Leu Pro Ile Gly Lys Ser
 130 135 140

Gly Ser Leu Thr Cys His Leu Tyr Phe Pro Glu Ser Cys Val Leu Asp
 145 150 155 160

Ser Ile Lys Trp Tyr Lys Gly Cys Glu Glu Ile Lys Val Ser Lys Lys
 165 170 175

Phe Cys Pro Thr Gly Thr Lys Leu Leu Val Asn Asn Ile Asp Val Glu
 180 185 190

Asp Ser Gly Ser Tyr Ala Cys Ser Ala Arg Leu Thr His Leu Gly Arg
 195 200 205

Ile Phe Thr Val Arg Asn Tyr Ile Ala Val Asn Thr Lys Glu Val Gly
 210 215 220

Ser Gly Gly Arg Ile Pro Asn Ile Thr Tyr Pro Lys Asn Asn Ser Ile
 225 230 235 240

Glu Val Gln Leu Gly Ser Thr Leu Ile Val Asp Cys Asn Ile Thr Asp
 245 250 255

Thr Lys Glu Asn Thr Asn Leu Arg Cys Trp Arg Val Asn Asn Thr Leu
 260 265 270

Val Asp Asp Tyr Tyr Asn Asp Phe Lys Arg Ile Gln Glu Gly Ile Glu
 275 280 285

Thr Asn Leu Ser Leu Arg Asn His Ile Leu Tyr Thr Val Asn Ile Thr
 290 295 300

Phe Leu Glu Val Lys Met Glu Asp Tyr Gly His Pro Phe Thr Cys His
 305 310 315 320

Ala Ala Val Ser Ala Ala Tyr Ile Ile Leu Lys Arg Pro Ala Pro Asp
 325 330 335

Phe Arg Ala Tyr Leu Ile Gly Gly Leu Met Ala Phe Leu Leu Ala
 340 345 350

Val Ser Ile Leu Tyr Ile Tyr Asn Thr Phe Lys Val Asp Ile Val Leu
 355 360 365

Trp Tyr Arg Ser Thr Phe His Thr Ala Gln Ala Pro Asp Asp Glu Lys
 370 375 380

Leu Tyr Asp Ala Tyr Val Leu Tyr Pro Lys Tyr Pro Arg Glu Ser Gln
 385 390 395 400

Gly His Asp Val Asp Thr Leu Val Leu Lys Ile Leu Pro Glu Val Leu
 405 410 415

Glu Lys Gln Cys Gly Tyr Lys Leu Phe Ile Phe Gly Arg Asp Glu Phe
 420 425 430

Pro Gly Gln Ala Val Ala Ser Val Ile Asp Glu Asn Ile Lys Leu Cys
 435 440 445

Arg Arg Leu Met Val Leu Val Ala Pro Glu Thr Ser Ser Phe Ser Phe
 450 455 460

Leu Lys Asn Leu Thr Glu Glu Gln Ile Ala Val Tyr Asn Ala Leu Val
 465 470 475 480

Gln Asp Gly Met Lys Val Ile Leu Ile Glu Leu Glu Arg Val Lys Asp
 485 490 495

Tyr Ser Thr Met Pro Glu Ser Ile Gln Tyr Ile Arg Gln Lys His Gly
 500 505 510
 Ala Ile Gln Trp Asp Gly Asp Phe Thr Glu Gln Ala Gln Cys Ala Lys
 515 520 525
 Thr Lys Phe Trp Lys Lys Val Arg Tyr His Met Pro Pro Arg Arg Tyr
 530 535 540
 Pro Ala Ser Pro Pro Val Gln Leu Leu Gly His Thr Pro Arg Ile Pro
 545 550 555 560
 Gly

(2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 567 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Ile Asp Arg Gln Arg Met Gly Leu Trp Ala Leu Ala Ile Leu Thr
 1 5 10 15
 Leu Pro Met Tyr Leu Thr Val Thr Glu Gly Ser Lys Ser Ser Trp Gly
 20 25 30
 Leu Glu Asn Glu Ala Leu Ile Val Arg Cys Pro Gln Arg Gly Arg Ser
 35 40 45
 Thr Tyr Pro Val Glu Trp Tyr Tyr Ser Asp Thr Asn Glu Ser Ile Pro
 50 55 60
 Thr Gln Lys Arg Asn Arg Ile Phe Val Ser Arg Asp Arg Leu Lys Phe
 65 70 75 80
 Leu Pro Ala Arg Val Glu Asp Ser Gly Ile Tyr Ala Cys Val Ile Arg
 85 90 95
 Ser Pro Asn Leu Asn Lys Thr Gly Tyr Leu Asn Val Thr Ile His Lys
 100 105 110
 Lys Pro Pro Ser Cys Asn Ile Pro Asp Tyr Leu Met Tyr Ser Thr Val
 115 120 125
 Arg Gly Ser Asp Lys Asn Phe Lys Ile Thr Cys Pro Thr Ile Asp Leu
 130 135 140
 Tyr Asn Trp Thr Ala Pro Val Gln Trp Phe Lys Asn Cys Lys Ala Leu
 145 150 155 160
 Gln Glu Pro Arg Phe Arg Ala His Arg Ser Tyr Leu Phe Ile Asp Asn
 165 170 175

Val Thr His Asp Asp Glu Gly Asp Tyr Thr Cys Gln Phe Thr His Ala
 180 185 190
 Glu Asn Gly Thr Asn Tyr Ile Val Thr Ala Thr Arg Ser Phe Thr Val
 195 200 205
 Glu Glu Lys Gly Phe Ser Met Phe Pro Val Ile Thr Asn Pro Pro Tyr
 210 215 220
 Asn His Thr Met Glu Val Glu Ile Gly Lys Pro Ala Ser Ile Ala Cys
 225 230 235 240
 Ser Ala Cys Phe Gly Lys Gly Ser His Phe Leu Ala Asp Val Leu Trp
 245 250 255
 Gln Ile Asn Lys Thr Val Val Gly Asn Phe Gly Glu Ala Arg Ile Gln
 260 265 270
 Glu Glu Glu Gly Arg Asn Glu Ser Ser Ser Asn Asp Met Asp Cys Leu
 275 280 285
 Thr Ser Val Leu Arg Ile Thr Gly Val Thr Glu Lys Asp Leu Ser Leu
 290 295 300
 Glu Tyr Asp Cys Leu Ala Leu Asn Leu His Gly Met Ile Arg His Thr
 305 310 315 320
 Ile Arg Leu Arg Arg Lys Gln Pro Ile Asp His Arg Ser Ile Tyr Tyr
 325 330 335
 Ile Val Ala Gly Cys Ser Leu Leu Leu Met Phe Ile Asn Val Leu Val
 340 345 350
 Ile Val Leu Lys Val Phe Trp Ile Glu Val Ala Leu Phe Trp Arg Asp
 355 360 365
 Ile Val Thr Pro Tyr Lys Thr Arg Asn Asp Gly Lys Leu Tyr Asp Ala
 370 375 380
 Tyr Ile Ile Tyr Pro Arg Val Phe Arg Gly Ser Ala Ala Gly Thr His
 385 390 395 400
 Ser Val Glu Tyr Phe Val His His Thr Leu Pro Asp Val Leu Glu Asn
 405 410 415
 Lys Cys Gly Tyr Lys Leu Cys Ile Tyr Gly Arg Asp Leu Leu Pro Gly
 420 425 430
 Gln Asp Ala Ala Thr Val Val Glu Ser Ser Ile Gln Asn Ser Arg Arg
 435 440 445
 Gln Val Phe Val Leu Ala Pro His Met Met His Ser Lys Glu Phe Ala
 450 455 460
 Tyr Glu Gln Glu Ile Ala Leu His Ser Ala Leu Ile Gln Asn Asn Ser
 465 470 475 480
 Lys Val Ile Leu Ile Glu Met Glu Pro Leu Gly Glu Ala Ser Arg Leu
 485 490 495
 Gln Val Gly Asp Leu Gln Asp Ser Leu Gln His Leu Val Lys Ile Gln
 500 505 510

Gly Thr Ile Lys Trp Arg Glu Asp His Val Ala Asp Lys Gln Ser Leu
 515 520 525
 Ser Ser Lys Phe Trp Lys His Val Arg Tyr Gln Met Pro Val Pro Glu
 530 535 540
 Arg Ala Ser Lys Thr Ala Ser Val Ala Ala Pro Leu Ser Gly Lys Ala
 545 550 555 560
 Cys Leu Asp Leu Lys His Phe
 565

(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 328 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Met Gly Phe Trp Ile Leu Ala Ile Leu Thr Ile Leu Met Tyr Ser Thr
 1 5 10 15
 Ala Ala Lys Phe Ser Lys Gln Ser Trp Gly Leu Glu Asn Glu Ala Leu
 20 25 30
 Ile Val Arg Cys Pro Arg Gln Gly Lys Pro Ser Tyr Thr Val Asp Trp
 35 40 45
 Tyr Tyr Ser Gln Thr Asn Lys Ser Ile Pro Thr Gln Glu Arg Asn Arg
 50 55 60
 Val Phe Ala Ser Gly Gln Leu Leu Lys Phe Leu Pro Ala Glu Val Ala
 65 70 75 80
 Asp Ser Gly Ile Tyr Thr Cys Ile Val Arg Ser Pro Thr Phe Asn Arg
 85 90 95
 Thr Gly Tyr Ala Asn Val Thr Ile Tyr Lys Lys Gln Ser Asp Cys Asn
 100 105 110
 Val Pro Asp Tyr Leu Met Tyr Ser Thr Val Ser Gly Ser Glu Lys Asn
 115 120 125
 Ser Lys Ile Tyr Cys Pro Thr Ile Asp Leu Tyr Asn Trp Thr Ala Pro
 130 135 140
 Leu Glu Trp Phe Lys Asn Cys Gln Ala Leu Gln Gly Ser Arg Tyr Arg
 145 150 155 160
 Ala His Lys Ser Phe Leu Val Ile Asp Asn Val Met Thr Glu Asp Ala
 165 170 175
 Gly Asp Tyr Thr Cys Lys Phe Ile His Asn Glu Asn Gly Ala Asn Tyr
 180 185 190

Ser Val Thr Ala Thr Arg Ser Phe Thr Val Lys Asp Glu Gln Gly Phe
 195 200 205
 Ser Leu Phe Pro Val Ile Gly Ala Pro Ala Gln Asn Glu Ile Lys Glu
 210 215 220
 Val Glu Ile Gly Lys Asn Ala Asn Leu Thr Cys Ser Ala Cys Phe Gly
 225 230 235 240
 Lys Gly Thr Gln Phe Leu Ala Ala Val Leu Trp Gln Leu Asn Gly Thr
 245 250 255
 Lys Ile Thr Asp Phe Gly Glu Pro Arg Ile Gln Gln Glu Gly Gln
 260 265 270
 Asn Gln Ser Phe Ser Asn Gly Leu Ala Cys Leu Asp Met Val Leu Arg
 275 280 285
 Ile Ala Asp Val Lys Glu Glu Asp Leu Leu Leu Gln Tyr Asp Cys Leu
 290 295 300
 Ala Leu Asn Leu His Gly Leu Arg Arg His Thr Val Arg Leu Ser Arg
 305 310 315 320
 Lys Asn Pro Ser Lys Glu Cys Phe
 325

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 398 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met Leu Arg Leu Tyr Val Leu Val Met Gly Val Ser Ala Phe Thr Leu
 1 5 10 15
 Gln Pro Ala Ala His Thr Gly Ala Ala Arg Ser Cys Arg Phe Arg Gly
 20 25 30
 Arg His Tyr Lys Arg Glu Phe Arg Leu Glu Gly Glu Pro Val Ala Leu
 35 40 45
 Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala Ser Val Ser Pro Arg
 50 55 60
 Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val Pro Gly
 65 70 75 80
 Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp Leu Leu
 85 90 95
 Pro Ala Leu Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr Arg Asn
 100 105 110

Ala Ser Tyr Cys Asp Lys Met Ser Ile Glu Leu Arg Val Phe Glu Asn
 115 120 125

Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu Thr Leu
 130 135 140

Ser Thr Ser Gly Val Leu Val Cys Pro Asp Leu Ser Glu Phe Thr Arg
 145 150 155 160

Asp Lys Thr Asp Val Lys Ile Gln Trp Tyr Lys Asp Ser Leu Leu Leu
 165 170 175

Asp Lys Asp Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr His Leu
 180 185 190

Leu Val His Asp Val Ala Leu Glu Asp Ala Gly Tyr Tyr Arg Cys Val
 195 200 205

Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg Ser Ile
 210 215 220

Glu Leu Arg Ile Lys Lys Lys Glu Glu Thr Ile Pro Val Ile Ile
 225 230 235 240

Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu Thr Ile
 245 250 255

Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr Met Leu
 260 265 270

Trp Trp Thr Ala Asn Asp Thr His Ile Glu Ser Ala Tyr Pro Gly Gly
 275 280 285

Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn Glu Asn
 290 295 300

Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu Asp Leu
 305 310 315 320

His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe Gln Thr
 325 330 335

Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Trp Gly Ile
 340 345 350

Val Leu Ala Pro Leu Ser Leu Ala Phe Leu Val Leu Gly Gly Ile Trp
 355 360 365

Met His Arg Arg Cys Lys His Arg Thr Gly Lys Ala Asp Gly Leu Thr
 370 375 380

Val Leu Trp Pro His His Gln Asp Phe Gln Ser Tyr Pro Lys
 385 390 395

(2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 410 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Met Phe Ile Leu Leu Val Leu Val Thr Gly Val Ser Ala Phe Thr Thr
 1 5 10 15

Pro Thr Val Val His Thr Gly Lys Val Ser Glu Ser Pro Ile Thr Ser
 20 25 30

Glu Lys Pro Thr Val His Gly Asp Asn Cys Gln Phe Arg Gly Arg Glu
 35 40 45

Phe Lys Ser Glu Leu Arg Leu Glu Gly Glu Pro Val Val Leu Arg Cys
 50 55 60

Pro Leu Ala Pro His Ser Asp Ile Ser Ser Ser His Ser Phe Leu
 65 70 75 80

Thr Trp Ser Lys Leu Asp Ser Ser Gln Leu Ile Pro Arg Asp Glu Pro
 85 90 95

Arg Met Trp Val Lys Gly Asn Ile Leu Trp Ile Leu Pro Ala Val Gln
 100 105 110

Gln Asp Ser Gly Thr Tyr Ile Cys Thr Phe Arg Asn Ala Ser His Cys
 115 120 125

Glu Gln Met Ser Val Glu Leu Lys Val Phe Lys Asn Thr Glu Ala Ser
 130 135 140

Leu Pro His Val Ser Tyr Leu Gln Ile Ser Ala Leu Ser Thr Thr Gly
 145 150 155 160

Leu Leu Val Cys Pro Asp Leu Lys Glu Phe Ile Ser Ser Asn Ala Asp
 165 170 175

Gly Lys Ile Gln Trp Tyr Lys Gly Ala Ile Leu Leu Asp Lys Gly Asn
 180 185 190

Lys Glu Phe Leu Ser Ala Gly Asp Pro Thr Arg Leu Leu Ile Ser Asn
 195 200 205

Thr Ser Met Asp Asp Ala Gly Tyr Tyr Arg Cys Val Met Thr Phe Thr
 210 215 220

Tyr Asn Gly Gln Glu Tyr Asn Ile Thr Arg Asn Ile Glu Leu Arg Val
 225 230 235 240

Lys Gly Thr Thr Glu Pro Ile Pro Val Ile Ile Ser Pro Leu Glu
 245 250 255

Thr Ile Pro Ala Ser Leu Gly Ser Arg Leu Ile Val Pro Cys Lys Val
 260 265 270

Phe Leu Gly Thr Gly Thr Ser Ser Asn Thr Ile Val Trp Trp Leu Ala
 275 280 285

Asn Ser Thr Phe Ile Ser Ala Ala Tyr Pro Arg Gly Arg Val Thr Glu
 290 295 300

Gly Leu His His Gln Tyr Ser Glu Asn Asp Glu Asn Tyr Val Glu Val
 305 310 315 320

Ser Leu Ile Phe Asp Pro Val Thr Arg Glu Asp Leu His Thr Asp Phe
 325 330 335
 Lys Cys Val Ala Ser Asn Pro Arg Ser Ser Gln Ser Leu His Thr Thr
 340 345 350
 Val Lys Glu Val Ser Ser Thr Phe Ser Trp Ser Ile Ala Leu Ala Pro
 355 360 365
 Leu Ser Leu Ile Ile Leu Val Val Gly Ala Ile Trp Met Arg Arg Arg
 370 375 380
 Cys Lys Arg Arg Ala Gly Lys Thr Tyr Gly Leu Thr Lys Leu Arg Thr
 385 390 395 400
 Asp Asn Gln Asp Phe Pro Ser Ser Pro Asn
 405 410

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 541 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Asn Cys Arg Glu Leu Pro Leu Thr Leu Trp Val Leu Ile Ser Val
 1 5 10 15
 Ser Thr Ala Glu Ser Cys Thr Ser Arg Pro His Ile Thr Val Val Glu
 20 25 30
 Gly Glu Pro Phe Tyr Leu Lys His Cys Ser Cys Ser Leu Ala His Glu
 35 40 45
 Ile Glu Thr Thr Lys Ser Trp Tyr Lys Ser Ser Gly Ser Gln Glu
 50 55 60
 His Val Glu Leu Asn Pro Arg Ser Ser Arg Ile Ala Leu His Asp
 65 70 75 80
 Cys Val Leu Glu Phe Trp Pro Val Glu Leu Asn Asp Thr Gly Ser Tyr
 85 90 95
 Phe Phe Gln Met Lys Asn Tyr Thr Gln Lys Trp Lys Leu Asn Val Ile
 100 105 110
 Arg Arg Asn Lys His Ser Cys Phe Thr Glu Arg Gln Val Thr Ser Lys
 115 120 125
 Ile Val Glu Val Lys Lys Phe Phe Gln Ile Thr Cys Glu Asn Ser Tyr
 130 135 140
 Tyr Gln Thr Leu Val Asn Ser Thr Ser Leu Tyr Lys Asn Cys Lys Lys
 145 150 155 160

Leu Leu Leu Glu Asn Asn Lys Asn Pro Thr Ile Lys Lys Asn Ala Glu
 165 170 175
 Phe Glu Asp Gln Gly Tyr Tyr Ser Cys Val His Phe Leu His His Asn
 180 185 190
 Gly Lys Leu Phe Asn Ile Thr Lys Thr Phe Asn Ile Thr Ile Val Glu
 195 200 205
 Asp Arg Ser Asn Ile Val Pro Val Leu Leu Gly Pro Lys Leu Asn His
 210 215 220
 Val Ala Val Glu Leu Gly Lys Asn Val Arg Leu Asn Cys Ser Ala Leu
 225 230 235 240
 Leu Asn Glu Glu Asp Val Ile Tyr Trp Met Phe Gly Glu Glu Asn Gly
 245 250 255
 Ser Asp Pro Asn Ile His Glu Glu Lys Glu Met Arg Ile Met Thr Pro
 260 265 270
 Glu Gly Lys Trp His Ala Ser Lys Val Leu Arg Ile Glu Asn Ile Gly
 275 280 285
 Glu Ser Asn Leu Asn Val Leu Tyr Asn Cys Thr Val Ala Ser Thr Gly
 290 295 300
 Gly Thr Asp Thr Lys Ser Phe Ile Leu Val Arg Lys Ala Asp Met Ala
 305 310 315 320
 Asp Ile Pro Gly His Val Phe Thr Arg Gly Met Ile Ile Ala Val Leu
 325 330 335
 Ile Leu Val Ala Val Val Cys Leu Val Thr Val Cys Val Ile Tyr Arg
 340 345 350
 Val Asp Leu Val Leu Phe Tyr Arg His Leu Thr Arg Arg Asp Glu Thr
 355 360 365
 Leu Thr Asp Gly Lys Thr Tyr Asp Ala Phe Val Ser Tyr Leu Lys Glu
 370 375 380
 Cys Arg Pro Glu Asn Gly Glu Glu His Thr Phe Ala Val Glu Ile Leu
 385 390 395 400
 Pro Arg Val Leu Glu Lys His Phe Gly Tyr Lys Leu Cys Ile Phe Glu
 405 410 415
 Arg Asp Val Val Pro Gly Gly Ala Val Val Asp Glu Ile His Ser Leu
 420 425 430
 Ile Glu Lys Ser Arg Arg Leu Ile Ile Val Leu Ser Lys Ser Tyr Met
 435 440 445
 Ser Asn Glu Val Arg Tyr Glu Leu Glu Ser Gly Leu His Glu Ala Leu
 450 455 460
 Val Glu Arg Lys Ile Lys Ile Ile Leu Ile Glu Phe Thr Pro Val Thr
 465 470 475 480
 Asp Phe Thr Phe Leu Pro Gln Ser Leu Lys Leu Leu Lys Ser His Arg
 485 490 495

Val Leu Lys Trp Lys Ala Asp Lys Ser Leu Ser Tyr Asn Ser Arg Phe
 500 505 510

Trp Lys Asn Leu Leu Tyr Leu Met Pro Ala Lys Thr Val Lys Pro Gly
 515 520 525

Arg Asp Glu Pro Glu Val Leu Pro Val Leu Ser Glu Ser . .
 530 535 540

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 537 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Met His His Glu Glu Leu Ile Leu Thr Leu Cys Ile Leu Ile Val Lys
 1 5 10 15

Ser Ala Ser Lys Ser Cys Ile His Arg Ser Gln Ile His Val Val Glu
 20 25 30

Gly Glu Pro Phe Tyr Leu Lys Pro Cys Gly Ile Ser Ala Pro Val His
 35 40 45

Arg Asn Glu Thr Ala Thr Met Arg Trp Phe Lys Gly Ser Ala Ser His
 50 55 60

Glu Tyr Arg Glu Leu Asn Asn Arg Ser Ser Pro Arg Val Thr Phe His
 65 70 75 80

Asp His Thr Leu Glu Phe Trp Pro Val Glu Met Glu Asp Glu Gly Thr
 85 90 95

Tyr Ile Ser Gln Val Gly Asn Asp Arg Arg Asn Trp Thr Leu Asn Val
 100 105 110

Thr Lys Arg Asn Lys His Ser Cys Phe Ser Asp Lys Leu Val Thr Ser
 115 120 125

Arg Asp Val Glu Val Asn Lys Ser Leu His Ile Thr Cys Lys Asn Pro
 130 135 140

Asn Tyr Glu Glu Leu Ile Gln Asp Thr Trp Leu Tyr Lys Asn Cys Lys
 145 150 155 160

Glu Ile Ser Lys Thr Pro Arg Ile Leu Lys Asp Ala Glu Phe Gly Asp
 165 170 175

Glu Gly Tyr Tyr Ser Cys Val Phe Ser Val His His Asn Gly Thr Arg
 180 185 190

Tyr Asn Ile Thr Lys Thr Val Asn Ile Thr Val Ile Glu Gly Arg Ser
 195 200 205

Lys Val Thr Pro Ala Ile Leu Gly Pro Lys Cys Glu Lys Val Gly Val
 210 215 220
 Glu Leu Gly Lys Asp Val Glu Leu Asn Cys Ser Ala Ser Leu Asn Lys
 225 230 235 240
 Asp Asp Leu Phe Tyr Trp Ser Ile Arg Lys Glu Asp Ser Ser Asp Pro
 245 250 255
 Asn Val Gln Glu Asp Arg Lys Glu Thr Thr Trp Ile Ser Glu Gly
 260 265 270
 Lys Leu His Ala Ser Lys Ile Leu Arg Phe Gln Lys Ile Thr Glu Asn
 275 280 285
 Tyr Leu Asn Val Leu Tyr Asn Cys Thr Val Ala Asn Glu Glu Ala Ile
 290 295 300
 Asp Thr Lys Ser Phe Val Leu Val Arg Lys Glu Ile Pro Asp Ile Pro
 305 310 315 320
 Gly His Val Phe Thr Gly Gly Val Thr Val Leu Val Leu Ala Ser Val
 325 330 335
 Ala Ala Val Cys Ile Val Ile Leu Cys Val Ile Tyr Lys Val Asp Leu
 340 345 350
 Val Leu Phe Tyr Arg Arg Ile Ala Glu Arg Asp Glu Thr Leu Thr Asp
 355 360 365
 Gly Lys Thr Tyr Asp Ala Phe Val Ser Tyr Leu Lys Glu Cys His Pro
 370 375 380
 Glu Asn Lys Glu Glu Tyr Thr Phe Ala Val Glu Thr Leu Pro Arg Val
 385 390 395 400
 Leu Glu Lys Gln Phe Gly Tyr Lys Leu Cys Ile Phe Glu Arg Asp Val
 405 410 415
 Val Pro Gly Gly Ala Val Val Glu Glu Ile His Ser Leu Ile Glu Lys
 420 425 430
 Ser Arg Arg Leu Ile Ile Val Leu Ser Gln Ser Tyr Leu Thr Asn Gly
 435 440 445
 Ala Arg Arg Glu Leu Glu Ser Gly Leu His Glu Ala Leu Val Glu Arg
 450 455 460
 Lys Ile Lys Ile Ile Leu Ile Glu Phe Thr Pro Ala Ser Asn Ile Thr
 465 470 475 480
 Phe Leu Pro Pro Ser Leu Lys Leu Leu Lys Ser Tyr Arg Val Leu Lys
 485 490 495
 Trp Arg Ala Asp Ser Pro Ser Met Asn Ser Arg Phe Trp Lys Asn Leu
 500 505 510
 Val Tyr Leu Met Pro Ala Lys Ala Val Lys Pro Trp Arg Glu Glu Ser
 515 520 525
 Glu Ala Arg Ser Val Leu Ser Ala Pro
 530 535

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 576 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met	Glu	Asn	Met	Lys	Val	Leu	Leu	Gly	Leu	Ile	Cys	Leu	Met	Val	Pro
1					5					10				15	
Leu	Leu	Ser	Leu	Glu	Ile	Asp	Val	Cys	Thr	Glu	Tyr	Pro	Asn	Gln	Ile
					20				25				30		
Val	Leu	Phe	Leu	Ser	Val	Asn	Glu	Ile	Asp	Ile	Arg	Lys	Cys	Pro	Leu
					35				40			45			
Thr	Pro	Asn	Lys	Met	His	Gly	Asp	Thr	Ile	Ile	Trp	Tyr	Lys	Asn	Asp
					50			55			60				
Ser	Lys	Thr	Pro	Ile	Ser	Ala	Asp	Arg	Asp	Ser	Arg	Ile	His	Gln	Gln
					65			70			75			80	
Asn	Glu	His	Leu	Trp	Phe	Val	Pro	Ala	Lys	Val	Glu	Asp	Ser	Gly	Tyr
					85			90			95				
Tyr	Tyr	Cys	Ile	Val	Arg	Asn	Ser	Thr	Tyr	Cys	Leu	Lys	Thr	Lys	Val
					100			105			110				
Thr	Val	Thr	Val	Leu	Glu	Asn	Asp	Pro	Gly	Leu	Cys	Tyr	Ser	Thr	Gln
					115			120			125				
Ala	Thr	Phe	Pro	Gln	Arg	Leu	His	Ile	Ala	Gly	Asp	Gly	Ser	Leu	Val
					130			135			140				
Cys	Pro	Tyr	Val	Ser	Tyr	Phe	Lys	Asp	Glu	Asn	Asn	Glu	Leu	Pro	Glu
					145			150			155			160	
Val	Gln	Trp	Tyr	Lys	Asn	Cys	Lys	Pro	Leu	Leu	Asp	Asn	Val	Ser	
					165			170			175				
Phe	Phe	Gly	Val	Lys	Asp	Lys	Leu	Leu	Val	Arg	Asn	Val	Ala	Glu	Glu
					180			185			190				
His	Arg	Gly	Asp	Tyr	Ile	Cys	Arg	Met	Ser	Tyr	Thr	Phe	Arg	Gly	Lys
					195			200			205				
Gln	Tyr	Pro	Val	Thr	Arg	Val	Ile	Gln	Phe	Ile	Thr	Ile	Asp	Glu	Asn
					210			215			220				
Lys	Arg	Asp	Arg	Pro	Val	Ile	Leu	Ser	Pro	Arg	Asn	Glu	Thr	Ile	Glu
					225			230			235			240	
Ala	Asp	Pro	Gly	Ser	Met	Ile	Gln	Leu	Ile	Cys	Asn	Val	Thr	Gly	Gln
					245			250			255				
Phe	Ser	Asp	Leu	Val	Tyr	Trp	Lys	Trp	Asn	Gly	Ser	Glu	Ile	Glu	Trp
					260			265			270				

Asn Asp Pro Phe Leu Ala Glu Asp Tyr Gln Phe Val Glu His Pro Ser
 275 280 285
 Thr Lys Arg Lys Tyr Thr Leu Ile Thr Thr Leu Asn Ile Ser Glu Val
 290 295 300
 Lys Ser Gln Phe Tyr Arg Tyr Pro Phe Ile Cys Val Val Lys Asn Thr
 305 310 315 320
 Asn Ile Phe Glu Ser Ala His Val Gln Leu Ile Tyr Pro Val Pro Asp
 325 330 335
 Phe Lys Asn Tyr Leu Ile Gly Gly Phe Ile Ile Leu Thr Ala Thr Ile
 340 345 350
 Val Cys Cys Val Cys Ile Tyr Lys Val Phe Lys Val Asp Ile Val Leu
 355 360 365
 Trp Tyr Arg Asp Ser Cys Ser Gly Phe Leu Pro Ser Lys Ala Ser Asp
 370 375 380
 Gly Lys Thr Tyr Asp Ala Tyr Ile Leu Tyr Pro Lys Thr Leu Gly Glu
 385 390 395 400
 Gly Ser Phe Ser Asp Leu Asp Thr Phe Val Phe Lys Leu Leu Pro Glu
 405 410 415
 Val Leu Glu Gly Gln Phe Gly Tyr Lys Leu Phe Ile Tyr Gly Arg Asp
 420 425 430
 Asp Tyr Val Gly Glu Asp Thr Ile Glu Val Thr Asn Glu Asn Val Lys
 435 440 445
 Lys Ser Arg Arg Leu Ile Ile Leu Val Arg Asp Met Gly Gly Phe
 450 455 460
 Ser Trp Leu Gly Gln Ser Ser Glu Glu Gln Ile Ala Ile Tyr Asn Ala
 465 470 475 480
 Leu Ile Gln Glu Gly Ile Lys Ile Val Leu Leu Glu Leu Glu Lys Ile
 485 490 495
 Gln Asp Tyr Glu Lys Met Pro Asp Ser Ile Gln Phe Ile Lys Gln Lys
 500 505 510
 His Gly Val Ile Cys Trp Ser Gly Asp Phe Gln Glu Arg Pro Gln Ser
 515 520 525
 Ala Lys Thr Arg Phe Trp Lys Asn Leu Arg Tyr Gln Met Pro Ala Gln
 530 535 540
 Arg Arg Ser Pro Leu Ser Lys His Arg Leu Leu Thr Leu Asp Pro Val
 545 550 555 560
 Arg Asp Thr Lys Glu Lys Leu Pro Ala Ala Thr His Leu Pro Leu Gly
 565 570 575

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 569 amino acids
- (B) TYPE: amino acid

(C) STRANDEDNESS: not relevant
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Met Lys Val Leu Leu Arg Leu Ile Cys Phe Ile Ala Leu Leu Ile Ser
 1 5 10 15

Ser Leu Glu Ala Asp Lys Cys Lys Glu Arg Glu Glu Lys Ile Ile Leu
 20 25 30

Val Ser Ser Ala Asn Glu Ile Asp Val Arg Pro Cys Pro Leu Asn Pro
 35 40 45

Asn Glu His Lys Gly Thr Ile Thr Trp Tyr Lys Asp Asp Ser Lys Thr
 50 55 60

Pro Val Ser Thr Glu Gln Ala Ser Arg Ile His Gln His Lys Glu Lys
 65 70 75 80

Leu Trp Phe Val Pro Ala Lys Val Glu Asp Ser Gly His Tyr Tyr Cys
 85 90 95

Val Val Arg Asn Ser Ser Tyr Cys Leu Arg Ile Lys Ile Ser Ala Lys
 100 105 110

Phe Val Glu Asn Glu Pro Asn Leu Cys Tyr Asn Ala Gln Ala Ile Phe
 115 120 125

Lys Gln Lys Leu Pro Val Ala Gly Asp Gly Gly Leu Val Cys Pro Tyr
 130 135 140

Met Glu Phe Phe Lys Asn Glu Asn Asn Glu Leu Pro Lys Leu Gln Trp
 145 150 155 160

Tyr Lys Asp Cys Lys Pro Leu Leu Asp Asn Ile His Phe Ser Gly
 165 170 175

Val Lys Asp Arg Leu Ile Val Met Asn Val Ala Glu Lys His Arg Gly
 180 185 190

Asn Tyr Thr Cys His Ala Ser Tyr Thr Tyr Leu Gly Lys Gln Tyr Pro
 195 200 205

Ile Thr Arg Val Ile Glu Phe Ile Thr Leu Glu Glu Asn Lys Pro Thr
 210 215 220

Arg Pro Val Ile Val Ser Pro Ala Asn Glu Thr Met Glu Val Asp Leu
 225 230 235 240

Gly Ser Gln Ile Gln Leu Ile Cys Asn Val Thr Gly Gln Leu Ser Asp
 245 250 255

Ile Ala Tyr Trp Lys Trp Asn Gly Ser Val Ile Asp Glu Asp Asp Pro
 260 265 270

Val Leu Gly Glu Asp Tyr Tyr Ser Val Glu Asn Pro Ala Asn Lys Arg
 275 280 285

Arg Ser Thr Leu Ile Thr Val Leu Asn Ile Ser Glu Ile Glu Ser Arg
 290 295 300
 Phe Tyr Lys His Pro Phe Thr Cys Phe Ala Lys Asn Thr His Gly Ile
 305 310 315 320
 Asp Ala Ala Tyr Ile Gln Leu Ile Tyr Pro Val Thr Asn Phe Gln Lys
 325 330 335
 His Met Ile Gly Ile Cys Val Thr Leu Thr Val Ile Ile Val Cys Ser
 340 345 350
 Val Phe Ile Tyr Lys Ile Phe Lys Ile Asp Ile Val Leu Trp Tyr Arg
 355 360 365
 Asp Ser Cys Tyr Asp Phe Leu Pro Ile Lys Ala Ser Asp Gly Lys Thr
 370 375 380
 Tyr Asp Ala Tyr Ile Leu Tyr Pro Lys Thr Val Gly Glu Gly Ser Thr
 385 390 395 400
 Ser Asp Cys Asp Ile Phe Val Phe Lys Val Leu Pro Glu Val Leu Glu
 405 410 415
 Lys Gln Cys Gly Tyr Lys Leu Phe Ile Tyr Gly Arg Asp Asp Tyr Val
 420 425 430
 Gly Glu Asp Ile Val Glu Val Ile Asn Glu Asn Val Lys Lys Ser Arg
 435 440 445
 Arg Leu Ile Ile Ile Leu Val Arg Glu Thr Ser Gly Phe Ser Trp Leu
 450 455 460
 Gly Gly Ser Ser Glu Glu Gln Ile Ala Met Tyr Asn Ala Leu Val Gln
 465 470 475 480
 Asp Gly Ile Lys Val Val Leu Leu Glu Leu Glu Lys Ile Gln Asp Tyr
 485 490 495
 Glu Lys Met Pro Glu Ser Ile Lys Phe Ile Lys Gln Lys His Gly Ala
 500 505 510
 Ile Arg Trp Ser Gly Asp Phe Thr Gln Gly Pro Gln Ser Ala Lys Thr
 515 520 525
 Arg Phe Trp Lys Asn Val Arg Tyr His Met Pro Val Gln Arg Arg Ser
 530 535 540
 Pro Ser Ser Lys His Gln Leu Leu Ser Pro Ala Thr Lys Glu Lys Leu
 545 550 555 560
 Gln Arg Glu Ala His Val Pro Leu Gly
 565

(2) INFORMATION FOR SEQ ID NO:32:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 555 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met His Lys Met Thr Ser Thr Phe Leu Leu Ile Gly His Leu Ile Leu
1 5 10 15

Leu Ile Pro Leu Phe Ser Ala Glu Glu Cys Val Ile Cys Asn Tyr Phe
20 25 30

Val Leu Val Gly Glu Pro Thr Ala Ile Ser Cys Pro Val Ile Thr Leu
35 40 45

Pro Met Leu His Ser Asp Tyr Asn Leu Thr Trp Tyr Arg Asn Gly Ser
50 55 60

Asn Met Pro Ile Thr Thr Glu Arg Arg Ala Arg Ile His Gln Arg Lys
65 70 75 80

Gly Leu Leu Trp Phe Ile Pro Ala Ala Leu Glu Asp Ser Gly Leu Tyr
85 90 95

Glu Cys Glu Val Arg Ser Leu Asn Arg Ser Lys Gln Lys Ile Ile Asn
100 105 110

Leu Lys Val Phe Lys Asn Asp Asn Gly Leu Cys Phe Asn Gly Glu Met
115 120 125

Lys Tyr Asp Gln Ile Val Lys Ser Ala Asn Ala Gly Lys Ile Ile Cys
130 135 140

Pro Asp Leu Glu Asn Phe Lys Asp Glu Asp Asn Ile Asn Pro Glu Ile
145 150 155 160

His Trp Tyr Lys Glu Cys Lys Ser Gly Phe Leu Glu Asp Lys Arg Leu
165 170 175

Val Leu Ala Glu Gly Glu Asn Ala Ile Leu Ile Leu Asn Val Thr Ile
180 185 190

Gln Asp Lys Gly Asn Tyr Thr Cys Arg Met Val Tyr Thr Tyr Met Gly
195 200 205

Lys Gln Tyr Asn Val Ser Arg Thr Met Asn Leu Glu Val Lys Glu Ser
210 215 220

Pro Leu Lys Met Arg Pro Glu Phe Ile Tyr Pro Asn Asn Asn Thr Ile
225 230 235 240

Glu Val Glu Leu Gly Ser His Val Val Met Glu Cys Asn Val Ser Ser
245 250 255

Gly Val Tyr Gly Leu Leu Pro Tyr Trp Gln Val Asn Asp Glu Asp Val
260 265 270

Asp Ser Phe Asp Ser Thr Tyr Arg Glu Gln Phe Tyr Glu Glu Gly Met
275 280 285

Pro His Gly Ile Ala Val Ser Gly Thr Lys Phe Asn Ile Ser Glu Val
290 295 300

Lys Leu Lys Asp Tyr Ala Tyr Lys Phe Phe Cys His Phe Ile Tyr Asp
305 310 315 320

Ser Gln Glu Phe Thr Ser Tyr Ile Lys Leu Glu His Pro Val Gln Asn
 325 330 335
 Ile Arg Gly Tyr Leu Ile Gly Gly Ile Ser Leu Ile Phe Leu Leu
 340 345 350
 Phe Leu Ile Leu Ile Val Tyr Lys Ile Phe Lys Ile Asp Ile Val Leu
 355 360 365
 Trp Tyr Arg Ser Ser Cys His Pro Leu Leu Gly Lys Lys Val Ser Asp
 370 375 380
 Gly Lys Ile Tyr Asp Ala Tyr Val Leu Tyr Pro Lys Asn Arg Glu Ser
 385 390 395 400
 Cys Leu Tyr Ser Ser Asp Ile Phe Ala Leu Lys Ile Leu Pro Glu Val
 405 410 415
 Leu Glu Arg Gln Cys Gly Tyr Asn Leu Phe Ile Phe Gly Arg Asn Asp
 420 425 430
 Leu Ala Gly Glu Ala Val Ile Asp Val Thr Asp Glu Lys Ile His Gln
 435 440 445
 Ser Arg Arg Val Ile Ile Ile Leu Val Pro Glu Pro Ser Cys Tyr Gly
 450 455 460
 Ile Leu Glu Asp Ala Ser Glu Lys His Leu Ala Val Tyr Asn Ala Leu
 465 470 475 480
 Ile Gln Asp Gly Ile Lys Ile Ile Leu Ile Glu Leu Glu Lys Ile Glu
 485 490 495
 Asp Tyr Ala Asn Met Pro Glu Ser Ile Lys Tyr Val Lys Gln Lys Tyr
 500 505 510
 Gly Ala Ile Arg Trp Thr Gly Asp Phe Ser Glu Arg Ser His Ser Ala
 515 520 525
 Ser Thr Arg Phe Trp Lys Lys Val Arg Tyr His Met Pro Ser Arg Lys
 530 535 540
 His Gly Ser Ser Ser Gly Phe His Leu Ser Ser
 545 550 555

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 802 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Met Arg Leu Leu Leu Ala Leu Leu Gly Val Leu Leu Ser Val Pro Gly
 1 5 10 15

Pro	Pro	Val	Leu	Ser	Leu	Glu	Ala	Ser	Glu	Glu	Val	Glu	Leu	Glu	Pro
					20				25				30		
Cys	Leu	Ala	Pro	Ser	Leu	Glu	Gln	Gln	Glu	Gln	Glu	Leu	Thr	Val	Ala
					35				40				45		
Leu	Gly	Gln	Pro	Val	Arg	Leu	Cys	Cys	Gly	Arg	Ala	Glu	Arg	Gly	Gly
					50				55				60		
His	Trp	Tyr	Lys	Glu	Gly	Ser	Arg	Leu	Ala	Pro	Ala	Gly	Arg	Val	Arg
					65				70				75		80
Gly	Trp	Arg	Gly	Arg	Leu	Glu	Ile	Ala	Ser	Phe	Leu	Pro	Glu	Asp	Ala
					85				90				95		
Gly	Arg	Tyr	Leu	Cys	Leu	Ala	Arg	Gly	Ser	Met	Ile	Val	Leu	Gln	Asn
					100				105				110		
Leu	Thr	Leu	Ile	Thr	Gly	Asp	Ser	Leu	Thr	Ser	Ser	Asn	Asp	Asp	Glu
					115				120				125		
Asp	Pro	Lys	Ser	His	Arg	Asp	Pro	Ser	Asn	Arg	His	Ser	Tyr	Pro	Gln
					130				135				140		
Gln	Ala	Pro	Tyr	Trp	Thr	His	Pro	Gln	Arg	Met	Glu	Lys	Lys	Leu	His
					145				150				155		160
Ala	Val	Pro	Ala	Gly	Asn	Thr	Val	Lys	Phe	Arg	Cys	Pro	Ala	Ala	Gly
					165				170				175		
Asn	Pro	Thr	Pro	Thr	Ile	Arg	Trp	Leu	Lys	Asp	Gly	Gln	Ala	Phe	His
					180				185				190		
Gly	Glu	Asn	Arg	Ile	Gly	Gly	Ile	Arg	Leu	Arg	His	Gln	His	Trp	Ser
					195				200				205		
Leu	Val	Met	Glu	Ser	Val	Val	Pro	Ser	Asp	Arg	Gly	Thr	Tyr	Thr	Cys
					210				215				220		
Leu	Val	Glu	Asn	Ala	Val	Gly	Ser	Ile	Arg	Tyr	Asn	Tyr	Leu	Leu	Asp
					225				230				235		240
Val	Leu	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu	Pro
					245				250				255		
Ala	Asn	Thr	Thr	Ala	Val	Val	Gly	Ser	Asp	Val	Glu	Leu	Leu	Cys	Lys
					260				265				270		
Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Val
					275				280				285		
Ile	Asn	Gly	Ser	Ser	Phe	Gly	Ala	Val	Gly	Phe	Pro	Tyr	Val	Gln	Val
					290				295				300		
Leu	Lys	Thr	Ala	Asp	Ile	Asn	Ser	Ser	Glu	Val	Glu	Val	Leu	Tyr	Leu
					305				310				315		320
Arg	Asn	Val	Ser	Ala	Glu	Asp	Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly
					325				330				335		
Asn	Ser	Ile	Gly	Leu	Ser	Tyr	Gln	Ser	Ala	Trp	Leu	Thr	Val	Leu	Pro
					340				345				350		

Glu Glu Asp Pro Thr Trp Thr Ala Ala Ala Pro Glu Ala Arg Tyr Thr
 355 360 365
 Asp Ile Ile Leu Tyr Ala Ser Gly Ser Leu Ala Leu Ala Val Leu Leu
 370 375 380
 Leu Leu Ala Gly Leu Tyr Arg Gly Gln Ala Leu His Gly Arg His Pro
 385 390 395 400
 Arg Pro Pro Ala Thr Val Gln Lys Leu Ser Arg Phe Pro Leu Ala Arg
 405 410 415
 Gln Phe Ser Leu Glu Ser Gly Ser Ser Gly Lys Ser Ser Ser Ser Leu
 420 425 430
 Val Arg Gly Val Arg Leu Ser Ser Ser Gly Pro Ala Leu Leu Ala Gly
 435 440 445
 Leu Val Ser Leu Asp Leu Pro Leu Asp Pro Leu Trp Glu Phe Pro Arg
 450 455 460
 Asp Arg Leu Val Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln
 465 470 475 480
 Val Val Arg Ala Glu Ala Phe Gly Met Asp Pro Ala Arg Pro Asp Gln
 485 490 495
 Ala Ser Thr Val Ala Val Lys Met Leu Lys Asp Asn Ala Ser Asp Lys
 500 505 510
 Asp Leu Ala Asp Leu Val Ser Glu Met Glu Val Met Lys Leu Ile Gly
 515 520 525
 Arg His Lys Asn Ile Ile Asn Leu Leu Gly Val Cys Thr Gln Glu Gly
 530 535 540
 Pro Leu Tyr Val Ile Val Glu Cys Ala Ala Lys Gly Asn Leu Arg Glu
 545 550 555 560
 Phe Leu Arg Ala Arg Arg Pro Pro Gly Pro Asp Leu Ser Pro Asp Gly
 565 570 575
 Pro Arg Ser Ser Glu Gly Pro Leu Ser Phe Pro Val Leu Val Ser Cys
 580 585 590
 Ala Tyr Gln Val Ala Arg Gly Met Gln Tyr Leu Glu Ser Arg Lys Cys
 595 600 605
 Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn
 610 615 620
 Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Gly Val His His Ile
 625 630 635 640
 Asp Tyr Tyr Lys Lys Thr Ser Asn Gly Arg Leu Pro Val Lys Trp Met
 645 650 655
 Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val
 660 665 670
 Trp Ser Phe Gly Ile Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser
 675 680 685

Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Ser Leu Leu Arg Glu
690 695 700

Gly His Arg Met Asp Arg Pro Pro His Cys Pro Pro Glu Leu Tyr Gly
705 710 715 720

Leu Met Arg Glu Cys Trp His Ala Ala Pro Ser Gln Arg Pro Thr Phe
725 730 735

Lys Gln Leu Val Glu Ala Leu Asp Lys Val Leu Leu Ala Val Ser Glu
740 745 750

Glu Tyr Leu Asp Leu Arg Leu Thr Phe Gly Pro Tyr Ser Pro Ser Gly
755 760 765

Gly Asp Ala Ser Ser Thr Cys Ser Ser Ser Asp Ser Val Phe Ser His
770 775 780

Asp Pro Leu Pro Leu Gly Ser Ser Ser Phe Pro Phe Gly Ser Gly Val
785 790 795 800

Gln Thr

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6	C12N15/12	C12N15/62	C12N5/10	C07K14/715	C07K16/28
	C12Q1/68	A61K38/17	G01N33/577	G01N33/68	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D. BUCK: "Human DNA sequence from cosmid cU72E5, between markers DXS366 and DS87" EMBL SEQUENCE DATABASE, 24 December 1995, XP002099439 Heidelberg, FRG Accession no. Z68328, nucleotides 12206-12903; ---	28-30, 33
P, X	D. MUZNY ET AL.: "Xp22-164-166; HTG phase 1, 73 unordered pieces" EMBL SEQUENCE DATABASE, 5 October 1998, XP002099440 Heidelberg, FRG Accession no AC005748; --- -/-	28-30, 33

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search

12 April 1999

Date of mailing of the international search report

27.04.99

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hornig, H

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	T.L. BORN ET AL.: "Cloning of a novel receptor subunit, AcPL, required for interleukin-18 signalling" J. BIOL. CHEM., vol. 273, no. 45, 6 November 1998, pages 29445-29450, XP002091850 AM. SOC. BIOCHEM. MOL.BIOL.,INC.,BALTIMORE,US Accession nos.: AF07734 and AF077347; see the whole document ---	1-17
A	WO 96 07739 A (NEUROCRINE BIOSCIENCES INC) 14 March 1996 Sequence ID nos: 1-4; EMBL Sequence Accession nos.: U49066, U49065 see the whole document ---	1-37
A	P. PARNET ET AL.: "IL-1Rrp is similar to the type I interleukin-1 receptor and its homologues T1/ST2 and IL-1R AcP" J. BIOL. CHEM., vol. 271, no. 8, 23 February 1996, pages 3967-3970, XP002091852 AM. SOC. BIOCHEM. MOL.BIOL.,INC.,BALTIMORE,US Accession nos. U43672 and U43673 ---	1-37
A	T. TETSUKA ET AL.: "Nucleotide sequence of a complementary DNA for human ST2" EMBL SEQUENCE DATABASE, 3 September 1992, XP002091853 Heidelberg, FRG Accession no. D12763 ---	1-37
A	S. TOMINAGA : "A putative protein of a growth-specific cDNA from BALB/c-3T3cells is highly similar to the extracellular portion of mouse interleukin I receptor" FEBS LETTERS, vol. 258, 1989, pages 301-304, XP002091854 ELSEVIER, AMSTERDAM, NL Accession no. Y07519 see figure 3 ---	1-37
A	S.A. GREENFEDER ET AL.: "Molecular cloning and characterization of a second subunit of the interleukin 1 receptor complex" J. BIOL. CHEM., vol. 270, no. 23, 9 June 1995, pages 13757-13756, XP002091874 AM. SOC. BIOCHEM. MOL.BIOL.,INC.,BALTIMORE,US Accession no.X85999 see figure 1 ---	1-37

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	C.J. MCMAHAN ET AL.: "A novel IL-1 receptor, cloned from B cells by mammalian expression, is expressed in many cell types" EMBO J., vol. 10, no. 10, October 1991, pages 2821-2832, XP002091855 OXFORD UNIVERSITY PRESS, GB; see figure 3A ---	1-37
A	A.O. CHUA AND U. GUBLER: "Sequence of the cDNA for the human fibroblast type interleukin-1 receptor" NUCLEIC ACIDS RESEARCH, vol. 17, no. 23, 11 December 1989, page 10114 XP002091875 IRL PRESS LIMITED, OXFORD, ENGLAND Accession no.X16896 see the whole document ---	1-37
A	J.E. SIMS ET AL.: "cDNA expression cloning of the IL-1 receptor, a member of the immunoglobulin superfamily" SCIENCE, vol. 241, 29 July 1988, pages 585-589, XP002091876 AAAS, WASHINGTON, DC, US Accession no.M20658 see the whole document -----	1-37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/20939

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 16,26 and 17,36 (as far as an in vivo method is concerned) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-17

An isolated or recombinant human and/or mouse IL-1RD9 polypeptide: a) consisting of SEQ ID NOS.: 6,8,10,12,14 or 16; b) encoded by a polynucleotide comprising the open reading frame of SEQ ID NOS.: 5,7,9,11,13 or 15; or c) encoded by a naturally occurring allelic variant of a polynucleotide comprising the open reading frame of SEQ ID NOS.: 5,7,9,11,13 or 15; a fusion protein comprising said polypeptides; a composition comprising said polypeptides; a kit comprising said polypeptides; a method of raising an antibody, comprising immunizing an animal with said polypeptides; a method for producing an antibody:antigen complex using said polypeptides;

2. Claims: (18-37) partially

A composition of matter selected from the group of: a substantially pure or recombinant human IL-1RD8 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO. 4; a fusion protein comprising said IL-1RD8, respectively SEQ ID NOS.: 2 and 4; a kit comprising said polypeptides; a binding compound comprising an antigen binding site from an antibody, which specifically binds to a natural IL-1RD8 protein; a kit comprising said binding compound; a method of making an antibody comprising immunizing an immune system with an immunogenic amount of a human IL-1RD8 polypeptide; an isolated or recombinant nucleic acid compound encoding said human IL-1RD8; or said nucleic acid comprises a plurality of nonoverlapping segments of at least 15 nucleotides from SEQ ID NOS: 1 and 3; a cell transfected or transformed with said recombinant nucleic acid; a kit comprising said nucleic acid; 1 a method of making a human IL-1RD8 using said nucleic acids; a nucleic acid which hybridizes to SEQ ID NO. 3; a method of modulating physiology or development of a cell or tissue culture cells comprising contacting said cell with an agonist or antagonist of a human IL-1RD8;

3. Claims: (18-37) partially

Idem as invention 2 but limited to human IL-1RD10, respectively SEQ ID NOS.: 17-20;

Information on patent family members

Int'l Application No

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9607739	A 14-03-1996	AU 3680595	A 27-03-1996	A